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FORMULATION, DEVELOPMENT AND EVALUATION OF GASTRO RETENTIVE TABLET OF CARVEDILOL

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Abstract: The floating tablets of Carvedilol using **32** factorial design. Carvedilol is nonselective **α1-β1**-blocking agent belongs to BCS Class-II and Indicated for treatment of Hypertension/moderate Heart Failure.Beta blocker antagonize the effect of sympathetic nerve stimulation or circulating catecholamine at beta adrenoreceptor. Which ar widely distributed throughout body system. they also decrease plasma markers of activation it of sympathetic and thus beta blockers are set to possess intrinsic sympathomimetic activity. Gastroretentive dosage forms (GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal tract and improve the bioavailability of medications those are characterized by a narrow absorption window. The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. This review explains briefly about types of floating system, advantages, limitation, floating mechanism, factors affecting floating system, drug candidates suitable for floating, evaluation parameters and applicationof the system.

Key words: Carvedilol, Gastroretentive Floating tablet, xanthum gum, Sodium bicarbonate, floating lag time.

INTRODUCTION: Oral administration is seen to be the most promising method of drug delivery. Factors including gastric empting, gastrointestinal transit duration of dosage form, drug release from dosage form, and drug absorption site can all affect how effective an oral drug delivery system. The majority of oral dose forms have physiological limitations such as irregular gastrointestinal transit due to varying gastric empting, which results in a non-uniform absorption profile, partial drug release, and a shorter duration in the stomach. Several factors influence the gastric emptying of dosage forms in humans, resulting in wide inter- and intrasubject variations. Because many medications are absorbed well in the upper

gastrointestinal tract, As a result of the considerable variability, non-uniform absorption may occur, making bioavailability unpredictable. As a result, a helpful delivery system is one that can manage and prolong gastric emptying time while also delivering medications in larger concentrations to the absorption site (i.e. upper part of the small intestine)

1.1 Gastroretentive drug delivery system

The most convenient and favoured method of drug delivery to the systemic circulation is oral administration. Oral controlled release drug delivery has lately gained popularity in the pharmaceutical industry as a means of achieving increased therapeutic benefits such as convenience of dosage administration, patient compliance, and formulation flexibility. Drugs with short half-lives and easy absorption from the gastrointestinal tract (GIT) are swiftly removed from the systemic circulation. To obtain adequate therapeutic efficacy, these medicines must be dosed often.[1]To overcome this constraint, oral sustained-controlled-releaseformulations are being developed in an attempt to slowly release the drug into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time.Such a drug delivery would be held in the stomach after oral administration and release the medication in a regulated manner, allowing the drug to be delivered constantly to its absorption sites in the gastrointestinal tract (GIT). The short gastric retention time (GRT) and unpredictable short gastric emptying time (GET) of these drug delivery systems can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine), resulting in diminished efficacy of theadministered dose. It is desirable to achieve a longer stomach residence duration by the drug delivery in order to develop a site-specific orally administered controlled release dosage form.Prolonged stomach retention improves bioavailability, extends medication release time, decreases drug waste, and increases the solubility of drugs that are less soluble in a high pH environment. Prolonged gastric retention time (GRT) in the stomach may also be beneficialfor local action in the upper section of the small intestine, such as peptic ulcer treatment, and so on. Gastroretentive drug delivery is a method of extending the time a drug spends in the stomach, allowing for site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can stay in the gastrointestinal region for a long time, extending the gastric retention time (GRT) of medications significantly.

1.1.2 Approaches to achieve gastric retention

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including;

♣ Floating system,

♣ Swelling and expanding systems,

♣Bioadhesive systems,

♣ Modified-shape systems,

♣ High-density systems

1.1.3 Floating Drug Delivery Systems:

Floating systems are low-density devices with enough buoyancy to float above gastric contents and stay in the stomach for an extended period of time. The medicine is delivered slowly at the correct pace while the system floats over the gastric contents, resulting in increased gastro-retention time and less volatility.There are two types of FDDS systems: non- effervescent and gas-generating (effervescent).

1.1.4 Gas-generating Systems:

In this distribution system, effervescent interactions between carbonate/bicarbonate salts and citric/tartaric acid liberate CO2, which becomes entrapped in the gelled hydrocolloid layer, lowering its specific gravity and causing it to float over the chime. Swellable polymers like methocel, polysaccharides like chitosan, and effervescent components like sodium bicarbonate, citric acid, and tartaric acid are used in these systems. According to reports, the ideal stoichiometric ratio of citric acid and sodium bicarbonate for gas production is 0.76:1. The most popular method for making these systems is to employ resin beads that have been loaded with bicarbonate and coated with ethyl cellulose. Water can pass through the covering, which is insoluble but permeable. As a result, carbon dioxide is released, which causes the beads to float in the stomach.Other approaches and materials that have been reported include highly swellable hydrocolloids and light mineral oils, a sodium alginate and sodium bicarbonate mixture, multiple unit floating pills that generate carbon dioxide when ingested, floating mini-capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, among others.

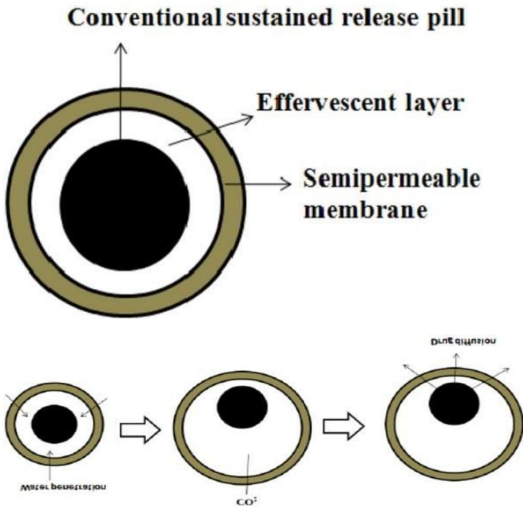


Fig 1 Effervescent (gas generating) system

1.2 Advantages of Floating Drug Delivery:

a) Improved bioavailability: When compared to non-GRDF CR polymeric formulations, the bioavailability of various medicines (e.g. riboflavin and levodopa) CR-GRDF is dramatically improved.

b) Improved biotransformation on the first pass:

The presystemic metabolism of the tested chemical may be significantly boosted when the medication is delivered to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4)in a sustained way rather than by a bolus intake.

c) Longer medication delivery/lower dose frequency:

A persistent and sluggish input from FDDS may result in a flip-flop pharmacokinetics and reduce the dose frequency for medicines with a short biological half-life. This trait is linked to increased patient compliance, which enhances therapy outcomes.

d) Targeted treatment for upper-GI-tract ailments:

1.3 Disadvantages of Floating Drug Delivery:

a) For drug administration to float and act well, these systems require a high amount of fluid in the stomach-coat, water

b) Incompatible with medications that have a problem with solubility or stability in the GI tract.

c) Drugs that are well absorbed throughout the GIT and undergo first-pass metabolism, such as Nifedipine, may not be desired.

d) Drugs that irritate the stomach mucosa are also undesirable or inappropriate.

e) Drugs that are unstable in the stomach's acidic environment are not ideal candidates forincorporation into the systems.

f) A full glass of water should be used to provide the dose form (200-250 ml) g) Thesesystems do not provide considerable benefits over traditional drug dosing formats.

1.4 Mechanism of Floating Systems:

Floating drug delivery systems (FDDS) have a lower bulk density than gastric fluids, therefore they float in the stomach for longer periods of time without altering the gastric emptying rate. The medicine is slowly released at the desired pace from the system while it is floating on the gastric contents.

The residual system in the stomach is emptied once the medicine is released. As a result, GRT is raised, and fluctuations in plasma drug concentration are better controlled. A minimumlevel of floating force (F) is also required to keep the dosage form stably buoyant on the surface of the meal, in addition to a minimum stomach content required to allow proper realisation of the buoyancy retention principle. to determine theA unique apparatus for determining resultant weight, floating force kinetics, has been reported in the literature.[10]

The equipment works by continually measuring the force necessary to keep the submerged object submerged (as a function of time). If F is on the positive side, the object floats better.

This device aids in the optimization of FDDS in terms of the stability and longevity of the floating forces produced, hence avoiding the disadvantages of unforeseen intragastric buoyancy capability fluctuations.

F = Fbuoyancy – Fgravity

= (Df - Ds) gv

Where, F= total vertical force,Df = fluid density,

Ds = Object density,v = Volume and

g = acceleration due to gravity

1.5 Application of Floating Drug Delivery Systems:

Because of the short absorption window in the upper gastrointestinal tract, floating medication delivery has various applications for medicines with low bioavailability. It keeps the dose form at the absorption site and so improves bioavailability. These are as follows: a. Sustained Medicine Delivery: HBS systems can stay in the stomach for lengthy periods of time, allowing the drug to be released over time. These approaches can thereby address the problem of a short gastric residence period that can occur with an oral CR formulation. These systems have a mass density of, allowing them to float on the contents of the stomach. Because these networks are relatively large, entering through the pyloric aperture is not permitted.

Sustained release floating capsules of nicardipine hydrochloride, for example, have been produced and tested in vivo. Rabbits were used to compare the formulation to commercially available MICARD capsules. In comparison to traditional MICARD capsules, the sustained release floating capsules had a longer administration time (16 hours) on plasma concentration time curves (8 hours)

b. Drug Delivery at a Specific Location: These systems are especially useful for medications that must be absorbed from the stomach or the small intestine's proximal section (Riboflavin and Furosemide) For example, furosemide is absorbed mostly by the stomach, followed bythe duodenum. A monolithic floating dosage form with a longer stomach residence time was devised, and the bioavailability was enhanced, according to the study. The AUC obtainedwith the floating pills was almost 1.8 times that of the fixed tablets conventional furosemide tablets.

MATERIALS AND METHODS:

2.1 List of the material and its role:

Material	Category
Carvedilol	Antihypertensive Drug
Xanthan gum	Gelling agent
Sodium bicarbonate	Alkalizing agent
Microcrystallinecellulose	Diluents
Steric acid	Lubricant
Citric acid	Acidifying agent
Magnesium stearate	Lubricant
Talc	Glidant

Table no 1 materials and their Role

2.2 PREFORMULATION STUDIES

2.2.1 Organoleptic properties:

Colour: a small quantity of pure carvedilol powder was taken in a butter paper and viewed in well illuminated place.

Taste and odour: very less quantity of carvedilol was used to get taste with the help of tongue as well as smelled to get the odour.

Solubility analysis:

Solubility is important pre-formulation parameter because it affects the dissolution and bio availability of drug.

Method: Solubility of carvedilol was determined in methanol, ethanol, dimethyl fluoride, methyl chloride, 0.1N HCl. Solubility studies were performed by taking excess amount of carvedilol in different beakers containing the solvent.

Melting point:

The melting point of carvedilol was determined by capillary method, using small quantity of carvedilol was taken and placed in apparatus and determined the melting point and matched with standards.

Loss on drying:

Determined on 0.50 g by drying in an oven at 100°C to 105°C for 3 hours. Mixed and accurately weighed the substance to be tested. Tare a glass stopper, shallow

weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Weighed the empty bottle (W1). Put the sample in bottle, replaced the cover, and accurately weighed the bottle with contents (W2). By gently, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature in desicator beforeweighing. Weighed the bottle (W3). The difference between successive weights should not less than 0.3%.

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2-W3)}{(W2-W1)} \times 100$$

Where, W1 = Weight of empty weighing bottleW2 = Weight of weighing bottle + sample

W3 = Weight of weighing bottle + dried sample

2.2.2 Drug powder characterization:

Angle of repose: Angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. The internal angle between the surface of the pile and horizontal surface is known as the angle of repose and is related to the density, surface area and co-efficient of friction of the raw material.

Method: Angle of repose was determined by using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Θ = tan-1 (h/r)

Where, h = height of heap, r = radius of heap, Θ = angle of repose

Bulk density:

Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density was increased. In addition, as the granule size increases bulk density decreases.

Method: A quantity of 5 gm of powder weighed and transferred to a measuring cylinder. The bulk volume and weight of the powder was determined.

Bulk density was calculated using the formula.

Bulk Density = Bulk Mass / Bulk VolumeTapped density:

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder. Then the tapping was done and the tapped volume was noted.

The tapped density was calculated by using the following formula:

Tapped Density = m/Vf

Where, m = initial weight of material in gm, Vf = volume of material after tapping. Generally replicate determinations are desirable for the determination of this property.

Measurement of Powder Compressibility:

Based on the apparent bulk and the tapped density, the percentage compressibility of bulk wasdetermined by the following formula.

(Vo –Vf)

Compressibility index*:* = 100----------

Vo

2.3 Standard calibration curve:

Determination of in UV range

The stock solution of drug sample was prepared by dissolving 10 mg of drug in 100 ml of 0.1NHCL, solution was diluted and analyzed spectrophotometrically between 400nm and 200nm

Preparation of standard calibration curve of carvedilol

The stock solution (100 µg/ml) was prepared by dissolving accurately weighed 10 mg of drug in 0.1N HCL. The solution in the concentration range 2-10µg/ml was prepared by appropriate dilution of the stock solution. The UV absorbance of these solution was recorded

2.4 Determination of Infrared absorption spectrum of carvedilol

The IR spectra of sample were recorded by potassium bromide dispersion technique. About 1-2 mg of sample was used. The baseline correction was carried out using 0.1 N HCL. The spectrum was recorded in the range 4000-400 cm-1 in the solid state and peak belonging to major functional groups were identified.

2.5 Preparation of Carvedilol Phosphate Floating Tablets:

All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and xanthan gum were blended geometrically in a mortar and pestle for 15 minutes then sodium bicarbonate, talc and magnesium stearate were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 44 mesh. Powder blend was compressed by using rotary tablet punching machine.

r.No	ngredient	F1	F2	F3	F4	F5
	Carvedilol	25	25	25	25	25
	Xanthan gum	25	25	00	00	00
	Sodium icarbonate	30	5	45	30	5
	Microcrystalline ellulose	62	77	72	87	02
	teric acid	0	0	0	0	0
	Citric acid	0	0	0	0	0
	Magnesium tearate					
	Talc					
	Total weight	00	00	00	00	00

Table no. 2 Formula for the preparation of carvedilol floating tablets.

2.6 Evaluation of floating tablets of carvedilol:

Tablet thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using Vernier calipers. The average thickness and standard deviation were reported.

Weight variation:

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits.

Tablet hardness:

Tablet hardness was measured using a Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness and standard deviation was reported.

Friability:

Twenty (20) tablets were selected from each batch and weighed. Each groupof tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

Content uniformity:

The formulated carvedilol floating tablets were assayed for drug content. From each batch of prepared tablets, ten tablets were collected randomly and powdered. a quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 100 ml of methanol was added and then the solution was subjected to sonication for about 2 hours.The solution was made up to the mark with methanol. The solution was filtered and suitable dilutions were prepared with methanol. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 240 nm by using UV-Visible spectrophotometer.

Buoyancy / Floating Test:

The *in vitro* buoyancy was determined by floating lag time. the tablets were placed in a 100- ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

2.7 Dissolution study of tablets:

Apparatus: Dissolution test apparatus (USP XXIII) Method: USP type 2 apparatus (paddle method) Dissolution medium: 0.1N HCl

Volume: 900 ml Temperature: 37 + 0.5 Speed: 50 rpm

Procedure

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 1,2,3,4,5,6,7,8,9,10,11,12 Hrs. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling. The release studies were conducted with 6 tablets, &determine the mean value. Then the mean values were plotted against time. Each sample was analyzed at 240nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve.

2.8 kinetic data analysis:

The analysis of drug release mechanism from a pharmaceutical dosage from is important but complicated process and is practically evident in the case of matrix systems. As a model- dependent approach, the dissolution

data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first order kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and Peppas-Korsemeyer equation.

Zero Order Release Kinetics:

It defined a linear relationship between the fractions of drug released versus time.

$Q = k_0 t$

Where, Q is the fraction of drug released at time t and ko is the zero-order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics

First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow-release tablets could be described adequately by apparent first- order kinetics. The equation that describes first order kinetics is

$\ln (1-Q) = - K_1 t$

Where, Q is the fraction of drug released at time t and k1 is the first order release rateconstant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if therelease obeys first order release kinetics.

Higuchi's equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) on thesquare root of time.

$Q=K_2 t^{1/2}$

Where, K2 is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

Korsmeyer peppas equation:

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppas and Korsemeyer equation (Power Law).

RESULT AND CONCLUSION:

3.1 Preformulation study:

These tests were performed as per procedure. The results were illustrated in table no.

3.1.1 Organoleptic properties:

Sr. no	Properties	Observation
	Colour	White

2	Odour	odourless

Table no 3 observation of organoleptic properties

3.1.2 Solubility analysis:

Sr.No	Solvent	Observation
1	Water	nsoluble
2	Methanol	Slightly soluble
3	0.1N HCL	oluble

Table no 4 observation of Solubility analysis

3.1.3 Melting point of drug:

The melting point of carvedilol was determined by capillary method, melting point of carvedilol was found to be 140°C - 127°C. Melting point compared with USP standards that showed that drug is pure

3.1.4 Loss on Drying:

Test	Observation
Loss on drying	0.8%

Table no.5 loss on drying

3.2 Drug powder characterization:

Batch code	Angle of repose	Bulk density gm/ml)	Tappeddensity gm/ml)	Carr`s compressibility ndex (%)	Hausner ratio
F1	27.50±0.19	0.442±0.12	0.505±0.09	12.47±1.12	1.14±0.03
F2	28.50±0.32	0.454±0.10	0.515±0.12	11.84±1.03	1.13±0.12
F3	28.85±0.36	0.446±0.07	0.520±0.08	14.23±1.15	1.16±0.05
F4	29.51±0.54	0.417±0.08	0.489±0.10	14.72±0.19	1.17±0.13
F5	27.15±0.29	0.433±0.11	0.525±0.09	17.52±0.25	1.21±0.08

Table no. 6 Pre-compression parameter of the tablet blend

3.3 Standard curve of carvedilol drug:

Calibration curve of carvedilol was determined by plotting absorbance (nm) versus concentration(µg/ml) at 240 nm. The result is obtained as follow.

Concentration (µg/ml)	Absorbance (nm)
5	0.185± 0.67
10	0.340±0.56
15	0.480±0.48

20	).570±0.81
25	).765±0.75
30	).890±0.58

n=3 ± SD

Table no 7 Standard curve of carvedilol

The linear regression analysis was done on absorbance data points. A straight line generated to facilitate the calculation of amount of drug, the equation is as follows:

Y = mx + c

Where Y=absorbance, m=slope, x=concentration

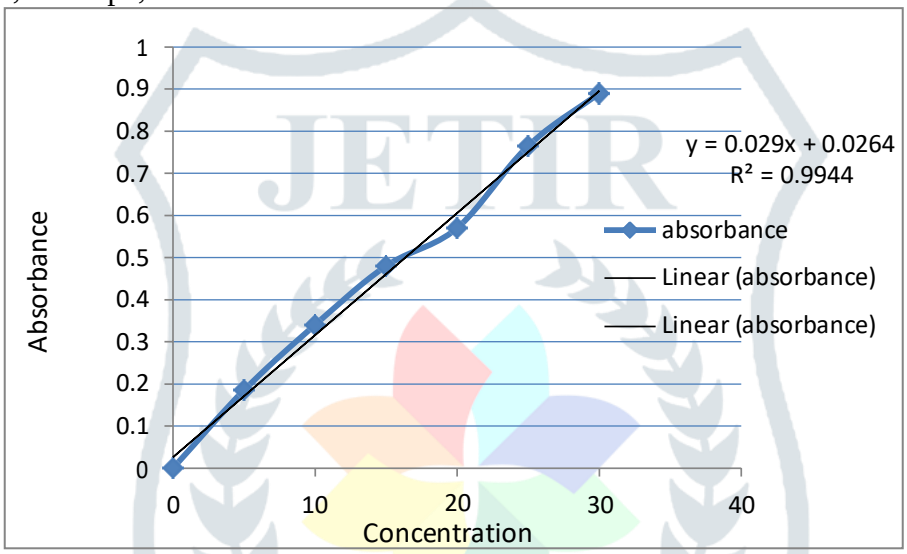
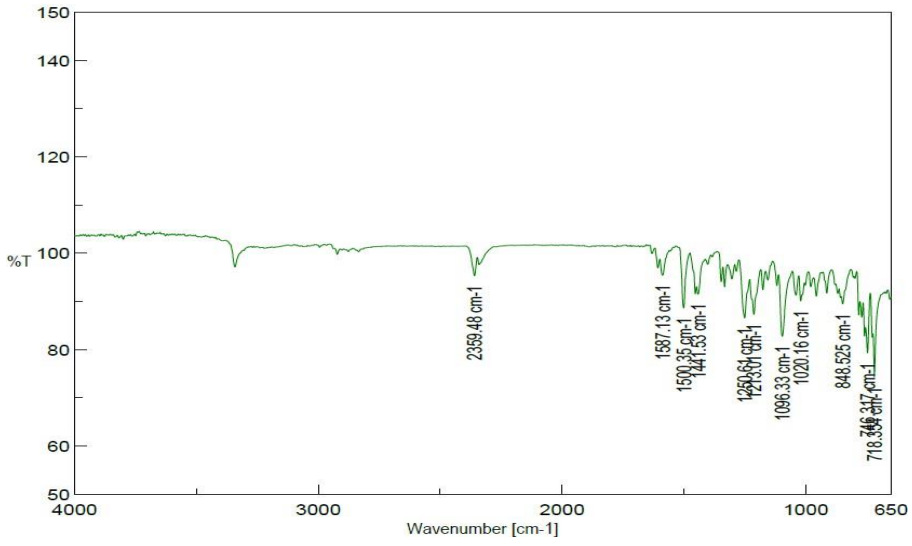


Fig 2 Standard plot for carvedilol in 0.1N HCL

3.4 Determination of Infrared absorption spectrum: Infrared absorption spectrophotometry of carvedilol:



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Sample name
Comment
User
Division
Company KBHSST,MALEGAON

[Measurement Information]
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Serial Number E154761786

Accessory ATR PRO ONE
Accessory S/N C167061809
Incident angle 45 deg

Measurement Date 30-05-2022 14:51

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Detector TGS
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Resolution 4 cm-1
Zero Filling On
Apodization Cosine
Gain Auto (8)
Aperture Auto (7.1 mm)
Scanning Speed Auto (2 mm/sec)
Filter Auto (30000 Hz)

Carvedilil IR.jws

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Date modified 30-05-2022 15:05

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Vertical axis %T
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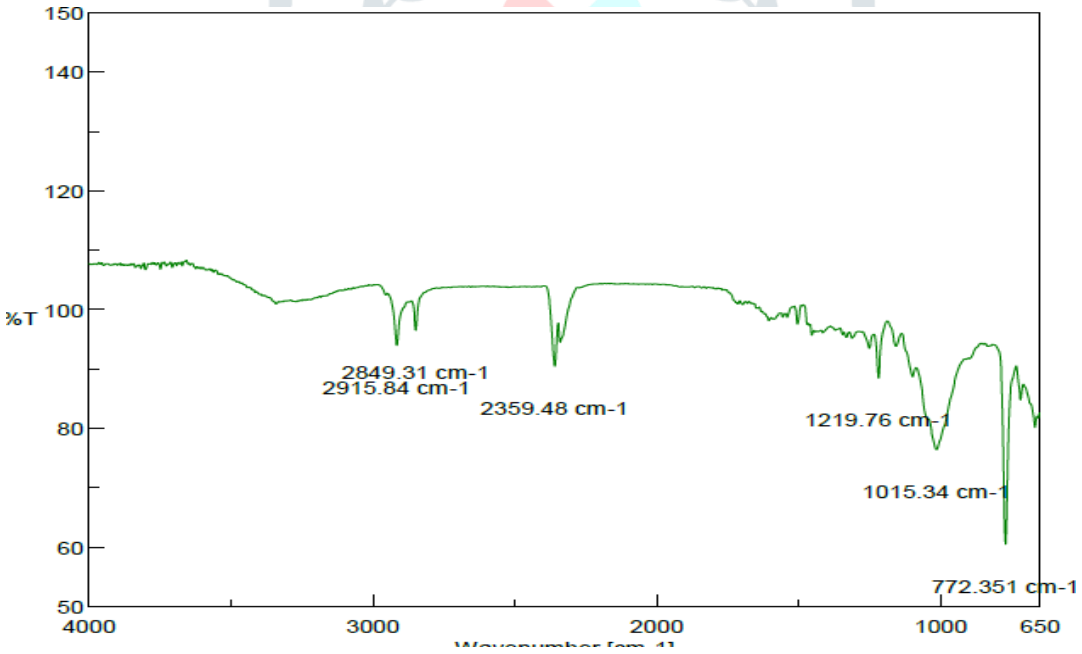
End 7800.65 cm-1
Data interval 0.964233 cm-1
Data points 7729

Fig No. 3 IR spectra of Carvidilol

r.no	ssignment	Observe value (cm-)	Reported value(cm-1)
	C-C stretching	096.33	00-1200
	-H stretching	500.35	200-1500
	C-O stretching	250.61	00-1300

Table no 8 characteristic peak of carvedilol



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User
Division
Company KBHSST,MALEGAON

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Serial Number E154761786

Accessory ATR PRO ONE
Accessory S/N C167061809
Incident angle 45 deg

Measurement Date 30-05-2022 14:56

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Detector TGS
Accumulation 16
Resolution 4 cm-1
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Gain Auto (8)
Aperture Auto (7.1 mm)
Scanning Speed Auto (2 mm/sec)
Filter Auto (30000 Hz)

Carved + Excepient.jws

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Data array type Linear data array
Horizontal axis Wavenumber [cm-1]
Vertical axis %T
Start 349.053 cm-1
End 7800.65 cm-1
Data interval 0.964233 cm-1
Data points 7729

Fig. No. 4 IR spectra of Carvidilol + Excipients

Sr.No	Assignment	Observe value (cm^{-1})	Reported value (cm^{-1})
1	C-C Stretching	1015.34	800-1200
2	O-H Stretching	3219.76	1200-1500
3	C-O Stretching	1219.76	1000-1300
4	C-HStretching	2915.84	2850-2975

Table no 9 characteristic peak of formulation mixture

3.5 Evaluation of formulated tablet:

Batch code	Hardness kg/cm2)	Thickness(mm)	Friability %)	Drug content %)	Weight variation %)
F1	3.2 ±0.34	4.66±0.21	0.64	95.56±0.19	99.12±2.99
F2	3.4 ±0.73	4.64±0.12	0.57	96.25±0.27	99.40±1.98
F3	3.3 ±0.28	4.67±0.25	0.64	93.50±0.41	99.36±3.7
F4	3.5 ±0.25	4.51±0.42	0.66	94.57±0.21	99.50±6.5
F5	3.3 ±0.36	4.59±0.23	0.54	97.20±0.26	99.90±1.6

Table no 10 Evaluation of formulated tablets.

Buoyancy / Floating Test: The tablets floated, while immersing in 0.1 N HCL solution PH (1.2) at 37 , and remained buoyant without disintegration. Table 20 showed the results of buoyancy study and shows buoyancy character of prepared tablet.

Sr. no	Batch no.	Lag time (min)	Total floating time(
1	F1	2.1±0.45	>12
2	F2	3.9±0.67	>12
3	F3	1.8±0.41	>12
4	F4	0.5±0.25	>12
5	F5	1.5±0.53	>12

n=3, ± SD

Table no.11 Lag time and mean floating time of different formulation batches

3.6 *In Vitro* Dissolution studies of tablets:

Dissolution study was carried out according to the procedure. The results were shown in fig no. Data for F1-F5 formulations given in table.

TIME	F1	F2	F3	F4	F5
)	)	)	)	)	)
	5.68±0.45	1.54±0.52	0.23±0.61	0.63±0.31	0.25±0.26
	6.22±0.75	3.10±0.48	1.77±0.25	4.75±0.90	1.55±0.50
	7.04±0.78	2.10±0.78	1.91±0.54	7.86±0.67	0.02±0.66
	5.23±0.54	6.20±0.66	2.77±0.76	2.01±0.43	0.35±0.76
	2.56±0.64	4.46±0.81	8.25±0.52	6.53±0.78	5.50±0.81
	1.70±0.43	2.90±0.64	3.15±0.47	1.66±0.32	1.05±0.52
	6.25±0.34	9.70±0.39	7.90±0.67	4.87±0.67	0.11±0.61
	5.63±0.83	5.40±0.89	2.32±0.86	6.52±0.89	5.16±0.40
)	7.26±0.89	8.54±0.65	1.30±0.56	0.25±0.56	3.14±0.49
0	8.45±0.24	2.02±0.86	4.42±0.27	4.20±0.35	0.58±0.66
1		5.26±0.71	9.67±0.38	7.02±0.76	3.25±0.53
2				9.64±0.45	8.47±0.46

Table no 12 In Vitro Dissolution study

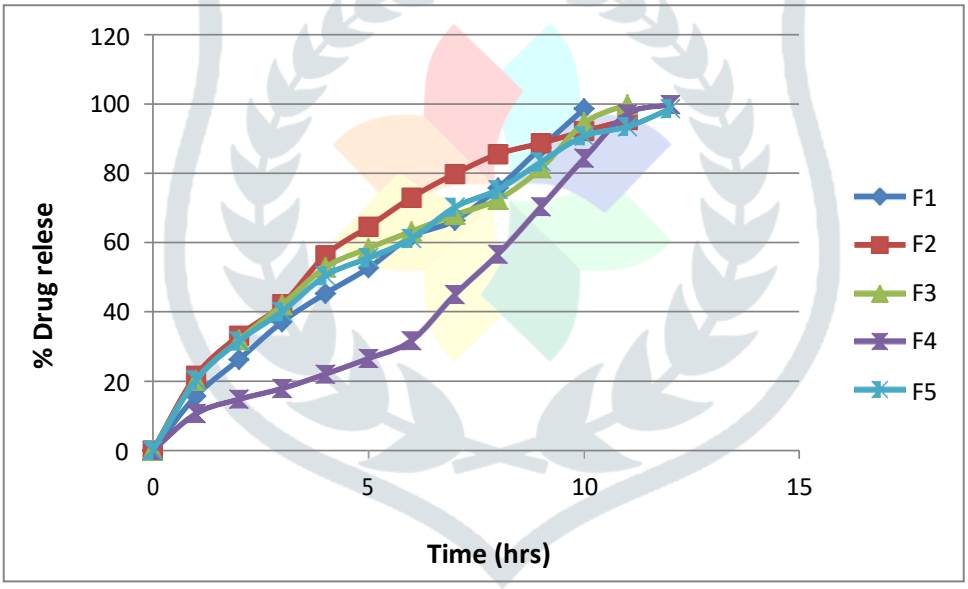

Fig no 5 dissolution profile

3.7 Kinetic studies of Optimize formulation:

Time (Hrs)	Log time	Zero order (cumulative %drug release)	First order (Log cumulative % drug release)	Higuchi plot (cumulative %drug relese)	Koresmeyer peppas plot (logcumulative % drug reles)
0	0	0	0	100	2.000
1	0	10.63±0.31	1.0265	89.37	1.9511
2	0.301	14.75±0.90	1.1687	85.25	1.9306
3	0.477	17.86±0.67	1.2518	82.14	1.9145
4	0.602	22.01±0.43	1.3426	77.99	1.8920
5	0.698	26.53±0.78	1.4237	73.47	1.8661
6	0.778	31.66±0.32	1.5005	68.34	1.8346
7	0.845	44.87±0.67	1.6519	55.13	1.7413
8	0.903	56.52±0.89	1.7522	43.48	1.6382
9	0.954	70.25±0.56	1.8466	29.75	1.4734
10	1.000	84.20±0.35	1.9235	15.8	1.1986
11	1.041	97.02±0.76	1.9868	2.98	0.4742
12	1.079	99.64±0.45	1.9984	0.36	-0.4436

Table no 13 kinetic study of Optimize formulationZero order release kinetic:

Fig no. 6 Zero order plot

First order release kinetic

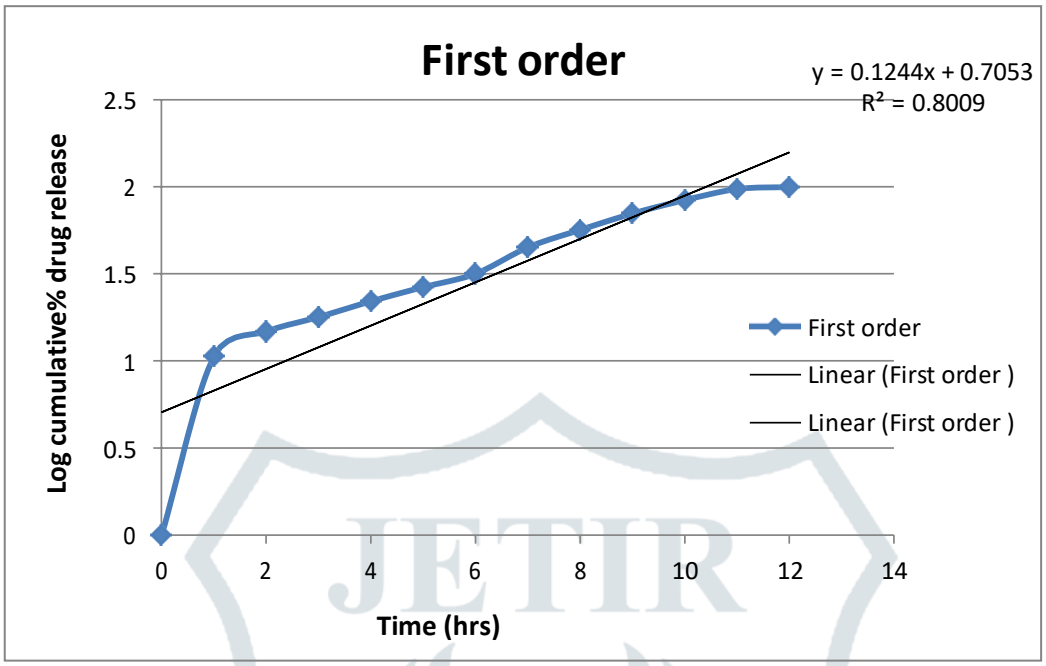

Fig no 7 First order plot

Higuchi plot:

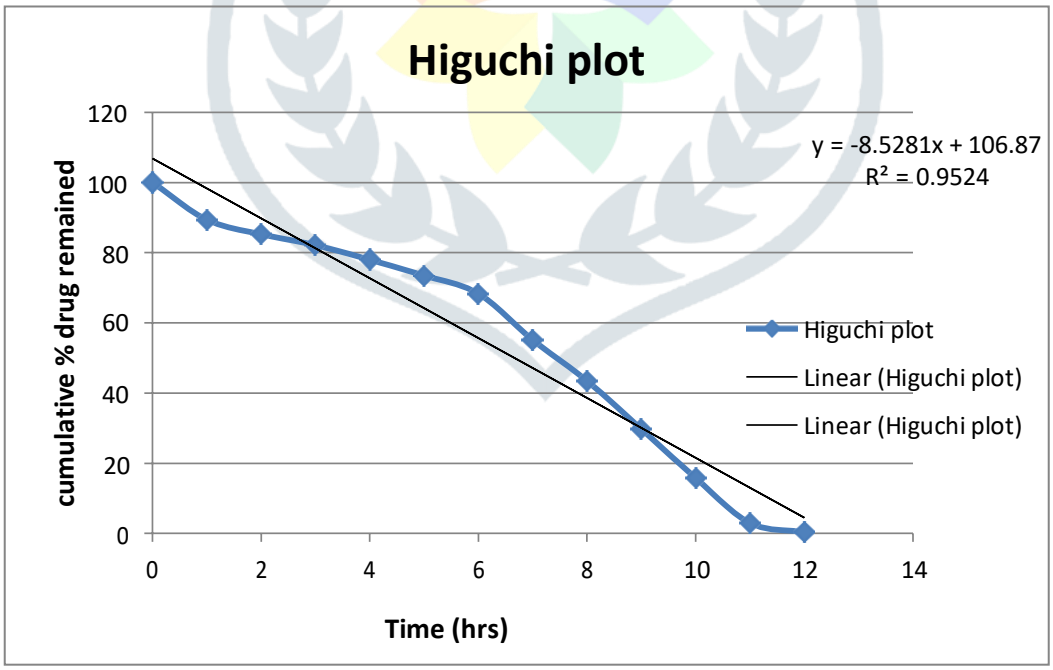

Fig no. 8 Higuchi plot

koresmeyer peppas plot:

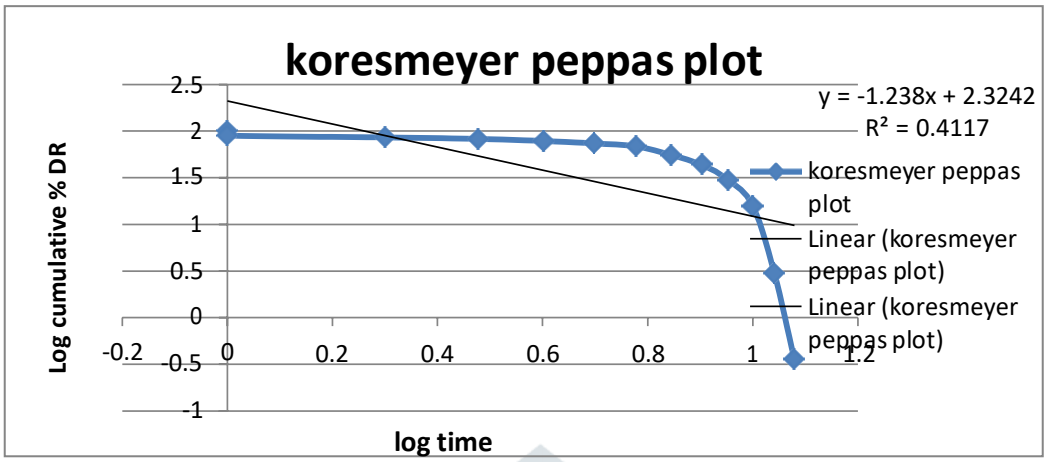

Fig no. 9 koresmeyer peppas plotSUMMARY AND CONCLUSION

The main objective of the present study was to develop floating formulation containing 25mg of carvedilol for once daily therapy by using natural polymers like xanthan gum. GRDDS improved the bioavailability and therapeutic efficiency of drug.

In the preformulation FTIR study was carried out for pure drug (carvedilol), carvedilol and excipients. It has not shown any interaction. Hence drugs were found to be compatible with excipients.

The formulations were prepared by direct compression method .The angle of repose valuesfor formulations range from 27.15 ± 0.29 to 29.51 ± 0.54.Bulk and tapped densities were used for the measurement of compressibility index .The bulk and tapped values for formulations range from 0.417 ± 0.08 to 0.454 ± 0.10 and 0.489 ± 0.10 to 0.525 ± 0.09 respectively.The carr's index and hausner's ratio values for formulations range from 12.47 ± 1.12 to 17.52 ±

0.25 and 1.13 ± 0.12 to 1.21 ± 0.08 respectively. Thus, all formulations exhibited good flow characteristics.

The prepared floating tablets were evaluated for various parameters like thickness, weight variation, hardness, friability and drug content uniformity. The thicknesses of tablets in all formulations were ranged from 4.51 ± 0.42 to 4.67 ± 0.25. The weight variations of tablets in all formulations were ranged from 399.12 ± 2.99 to 399.90±1.6. The hardness and friability ofall the formulations was found to be 3.2 ± 0.34 to 3.5 ± 0.73 kg/cm^2 and 0.54 to 0.66%respectively. Drug content of all the formulations were ranging from 93.50 ± 0.41 to 97.20 ± 0.26. The buoyancy lag time of all the formulations were ranging from 0.5.to 4.1 min.

Compared to all formulations F4 showed the best buoyancy lag time, the buoyancy lag time for F4 was found to 0.5 min. Total floating time of all formulations was found to be >12 hrs. The formulation containing xanthan gum.

The prepared tablets were then subjected to dissolution test for evaluating the invitro drug release.The dissolution studies were carried out in 0.1N Hcl in USP II apparatus at 37 ± 0.5 . The results of the dissolution studies indicated that the polymer concentration was having a substantial effect on the drug release from the tablets. Formulation F4 gave better floating properties incomparison to the other formulations. This formulation took 0.5 min to become buoyant.

The kinetic study was carried out for F4 formulation which showed that the drug release followed zero order kinetics followed by non-fickian diffusion.

Conclusion:

The present research work is the applicability a gas generating agent such as xanthum gum and sodium bicarbonate respectively in the design and development of gastroretentive floating tablet formulation of carvedilol.

From the above study, concluded that F4 was the optimized formulation which has shown better buoyancy time 0.5 min and drug release 99.64 % in 12 hrs. However, further in vivo studies can be carried out to support the results.

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