Original Research

DESIGN AND EVALUATION OF AN EFFERVESCENT GASTRO RETENTIVE DRUG DELIVERYSYSTEMOF CARVEDILOL USING GUMS

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ABSTRACT

The present investigation, GFDDS of Carvedilol were prepared with natural gums (guar gum, xanthan gum, okra gum) to deliver carvedilol to the upper parts of the small intestine in a controlled manner to improve its bioavailability. Gastric floating drug delivery systems offer numerous advantages over other gastric retention systems. Drug-excipient compatibility studies were proved by using FTIR. The effect of different formulation parameters such as concentrations of effervescent agent on floating properties and drug release kinetics were studied and the formulations were optimized. The correlation coefficients and the slope values from Higuchi plots indicated that the release mechanism followed diffusion and erosion with zero order kinetics. At lower concentration, gums acted as a rapid swelling agent and improved floating characteristics, but at higher concentration decreased the compactness of the tablet due to its disintegrant action and also log time. Hence, the different concentration of the gums was optimized to protect integrity of the tablet.From the results it can be concluded Xanthan gum and sodium bicarbonate as gas generating agent provides the 96.40% of drug release upto12hours.

KEY WORDS: GFDDS, Carvedilol, Guar gum, Okra gum, FTIR.

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INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form and site of absorption of drugs. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter and intra subject variations are observed[1]

Carvedilol is an orally administered beta adreno receptor antagonist widely used in the treatment of hypertension and chronic heart failure. It has a unique mechanism of action, proven efficacy and a favourable safety profile. The drug is commonly administered as oral tablets at high doses 2-3 times per day. The efforts have been focused on the development of controlled release gastric retention dosage forms. Hence in the present investigation, it is aimed to develop GFDDS of carvedilol (effervescent floating tablets) with three different grades of swellable polymers guar gum, xanthan gum, okar gum.

ADVANTAGES OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Gastro retentive drug delivery system has numerous advantages

The principle of HBS can be used for any particular medicament (or) class of medicament.The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salt and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g.chlorpheniramine.Gastric retention will provide advantages such as the delivery of drug with narrow absorption windows in the small intestinal region.The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.

DISADVANTAGES OF GASTRO RETENTIVE DRUG DELIVERY SYSTEMS

There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to causes gastric lesions and slow release of such drugs in the stomach is unwanted.Thus the drugs that may irritate the stomach lining (or) are unstable in its acidic environment should not be formulated in gastro retentive system.Furthermore, other drugs, such as isosorbidedinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

MATERIALS

Carvedilol was received a gift sample from micro lab, Hosur. Okar gum was received gift sample from micro lab, Hosur. Guar gum and Xanthan gum was purchased from colorcon Asia Pvt/Ltd., Goa , Sodium bicarbonate and poly vinyl pyrollidine-k-30 was purchased from Nice chemicals laboratory.

FORMULATION DEVELOPMENT

PREPARATION OF GASTRO RETENTIVE FLOATING TABLET

Floating tablets containing carvedilol were prepared by wet granulation technique using variable concentration of Guar gum, Xanthan gum, Okra gum and gas generating agent as sodium

bicarbonate.Different tablets formulations were prepared by wet granulation technique. All the powders were passed through 60 mesh sieve.Magnesium stearatewas finally added as glident and lubricant. The blend was directly compressed using tablet compression machine.Each tablet contained 40 mg carvedilol and other pharmaceutical ingredients as listed tablet at each section.

The composition of drug to polymer concentrations are given in the below table.

Table 1:Composition of formulation F1-F6

Ingredients	F1	F2	F3	F4	F5	F6
Carvedilol	40	40	40	40	40	40
Okar gum	10	-	-	20	-	-
Xanthan gum	-	10	-	-	20	-
Guar gum	-	-	10	-	-	20
Sodium bi carbonate	20	20	20	20	20	20
PVP-k-30	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5

Table 2:Composition of formulation F7-F12

Ingredients	F7	F8	F9	F10	F11	F12
Carvedilol	40	40	40	40	40	40
Okar gum	40	-	-	60	-	-
Xanthan gum	-	40	-	-	60	-
Guar gum	-	-	40	-	-	60
Sodium bi carbonate	20	20	20	20	20	20
PVP-k-30	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5

Table 3: Composition of formulation F13-F15

Ingredients	F13	F14	F15
Carvedilol	40	40	40
Xanthan gum	40	40	40
Sodium bi carbonate	10	15	30
PVP-k-30	5	5	5
Magnesium stearate	5	5	5

ANALYTICAL METHOD DEVELOPMENT

Preparation of standard solution for standard graph

50 mg of carvedilol was dissolved in methanol in a 50 ml volumetric flask and the solution was made upon the mark with methanol

Procedure

The standard solution of carvedilol was subsequently diluted with 0.1 N Hydrochloric acidto obtain a series of dilutions containing 1,2,3,4 and 5µg of carvedilol in 1ml solution and the absorbance of these solutions was measured at 240 nm in Spectrophotometer (UV Spectrophotometer) against corresponding blank. The concentration of carvedilol and the corresponding absorbance value were given in table.

EVALUATION OF POWDER BLEND

Angle of repose[6]

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\mathbf{Tan\theta = h/r}$$

Where, R= radius, h=height of the powder cone.

Table 4: Relationship between angle of repose and powder flow

S.NO	ANGLE OF REPOSE (DEGREES)	FLOW
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	40 and above	Very poor

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2gm of powder blend from each formula, previously shaken to break and agglomerates formed was introduced into 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following equations.

LBD = Weight of the powder blend /Untapped volume of the packing

TBD = Weight of the powder blend /Tapped volume of the packing

Compressibility Index

The compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's index is as below

Carr's Index (%) = [(TBD-LBD)×100)/TBD]

Table 5: Compressibility index range

S.NO	% COMPRESSIBILITY INDEX	FLOWABILITY
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair-passable
4	23-35	Poor
5	33-35	Very poor
6	>40	Very Very poor

Total Porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the inter molecular spaces, V)

$$\textbf{Porosity (\%)} = V_{bulk} - V/V_{bulk} \times 10$$

EVALUATION OF TABLETS

Weight Variation tablets

To study weight variation twenty tablets of the formulation were weighed using an electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1N Hcl the drug content was determined measuring the absorbance at 240 nm after suitable dilution using a systronics UV/ VIS double spectrophotometer.

HardnessHardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in $Kg/cm^{2.}$ Three tablets were randomly picked and hardness of the tablets was determined.

Thickness

The thickness of the tablets was determined by using Vernier Callipers. Five tablets were used, and average values were calculated.

Friability

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into Friabilator. The Friabilator was operated at 25 rpm for 4 minutes (or) run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by

$$\textbf{\%Friability} = 100\ (1-W_0/W)$$

% Friability of tablets less than 1% are considered acceptable.

***In vitro* buoyancy studies**

The in vitro buoyancy was determined by floating lag tie method described by Dave B.S. The tablets were placed in 250 mi beaker containing 0.1N Hcl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyant were measured. The time taken for dosage from o emerge on surface of medium called floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

***In vitro* dissolution studies**

The release rate of carvedilol from floating tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N Hcl, at 37 ± 0.5 ^{o}C and 50 rpm A sample (5 ml) of the solution was withdrawn from the dissolution apparatus 5, 10, 15, 30, 45, 60 min, 2hrs, 4hrs, 6hrs, 8hrs, 10hrs, 12hrs and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N Hcl. Absorbance of these solutions was measured at 240 nm using a Systronics UV/ Vis double beam spectrophotometer.

The result s of in vitro release profiles obtained for all the HBS formulations were fitted into four models of data treatment as follows,

Cumulative percent drug released versus time (zero-order kinetic model).Log cumulative percent drug remaining versus time (first –order kinetic model).Cumulative percent drug released versus square root of time (Higuchi's model).Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).

Zero order kinetics

A zero-order release would be predicated by the following equation.

$$A_t = A_o - K_o t \quad \text{.....1}$$

Where,A_t = Drug release at time't',A_o = Initial drug concentration,K_O = Zero-order rate constant (hr $^{-1}$)

First order Kinetics

A first-order release would be predicted by the following equation

$$\text{Log } C = \text{Log } C_o - Kt/2.303 \quad \text{.....2}$$

Where, C = Amount of drug remained at time't',C_o = Initial amount of drug

K = First-order rate constant (hr $^{-1}$).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follows First-order kinetics. The constant 'K' can be obtained by multiplying 2.303 with slope values.

Higuchi's Model

Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = Kt^{½} \quad \text{.....3}$$

Where,Q = Amount of drug released at time't', T = Time (hours) at which 'Q' amount of drug is released.

When the data is plotted according to equation-3 i.e., cumulative drug released versus square root of

time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'k'.

Korsmeyer and Pappas model

The release rates from controlled release polymeric matrices can be described by the equation (4) proposed by Korsmeyer et al.

$$Q = K_1 t^n \quad ....4$$

Q is the percentage of drug released at time't', K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusional exponent indicative of the release mechanism. Diffusion exponent and solute release mechanism for cylindrical shape.

COMPATABILITY STUDIES

DRUG EXCIPIENT COMPATABILITY STUDIES BY IR SPECTROSCOPY

The FTIR spectroscopic studies were carried out between drug and polymer physical mixtures. The FTIR was carried out for carvedilol and Xanthan gum. The results obtained by the physical mixtures compared with the physical mixtures compared with the standard and the results obtained.

RESULTS AND DISCUSSION

The effect of various formulation factors such as concentration of gums, effervescent agent on floating properties and release kinetics were studied to optimize the formulation. The floating lag time mainly depends up on the concentration of effervescent agent present in the matrix. In the present study sodium bicarbonate was used as effervescent agent, as it is cheap and safe.

STANDARD PLOT OF CARVEDILOL

Table 6: Calibration curve for the estimation of Carvedilol in 0.1N Hcl

S.No	Concentration (µg/Ml)	Absorbance(nm)
1	0	0
2	1	0.124
3	2	0.223
4	3	0.323
5	4	0.415
6	5	0.539

Fig.1: Standard Plot of Carvedilol at 240 nm.

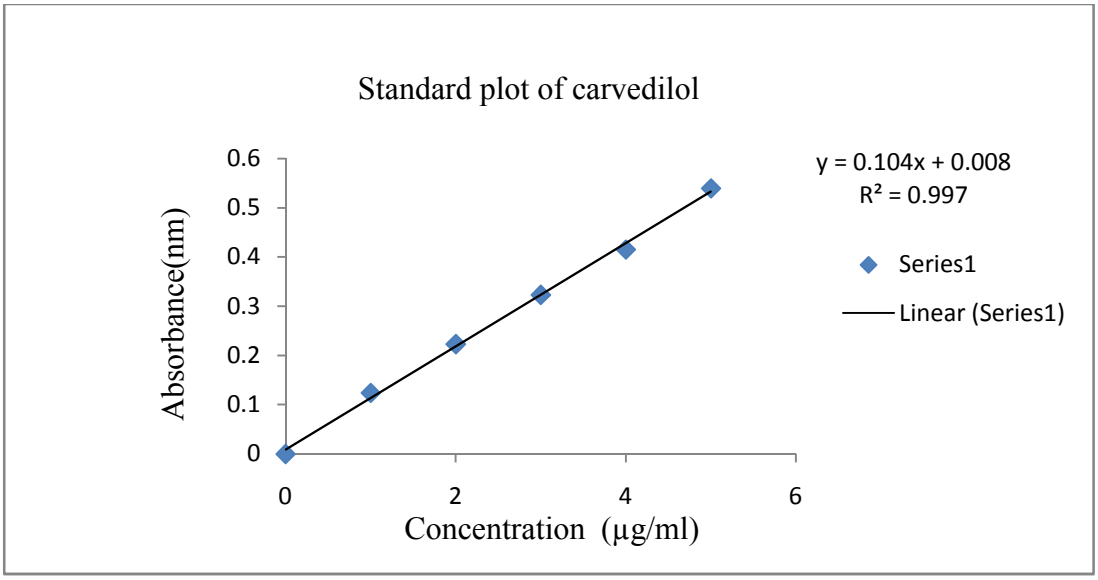


Table 7:Analytical parameters

S.no	Parameters	Values
1	Slope (m)	0.0856
2	Intercept (c)	0.003
3	Correlation coefficient (r)	0.9982
4	Beer's Law Range (µg/ml)	1 to 5
5	% RSD or % CV	0.486

Table 8: Assay values of the prepared formulations

Formulation	Buoyancy lag time (Sec)	Duration of floating (Hrs)
F1	75	>12
F2	60	>12
F3	50	>12
F4	60	>12
F5	50	>12
F6	50	>12
F7	45	>12
F8	55	>12
F9	80	>12
F10	40	>12
F11	40	>12
F12	60	>12
F13	50	>12
F14	65	>12
F15	40	>12

Table 9: Physical parameters of the prepared formulations

Formulation	Compressibility Index	Angle of repose
F1	13.25 ± 0.34	22.25 ± 0.12
F2	18.59 ± 0.12	21.16 ±0.31
F3	15.52 ± 0.14	36.52 ± 0.93
F4	17.86 ± 0.25	28.56 ± 0.34
F5	14.29 ± 0.32	22.82 ± 0.67
F6	17.84 ± 0.54	21.43 ± 0.89
F7	19.58 ±0.43	23.45 ± 0.41
F8	15.56 ± 0.61	22.47 ± 0.62
F9	14.78 ± 0.28	26.89 ± 0.64
F10	17.42 ± 0.32	27.45 ± 0.15
F11	18.56 ± 0.36	22.51 ± 0.41
F12	14.28 ± 0.53	21.85 ± 0.62
F13	18.09 ± 0.54	23.58 ± 0.54
F14	16.14 ± 0.81	24.57 ± 0.74
F15	17.25 ± 0.16	30.12 ± 0.34

Table 10: Comparative drug release profiles(F1-F6) at 240 nm

Time(hrs)	F1±SD	F2±SD	F3±SD	F4±SD	F5±SD	F6±SD
0.083	7.13±0.50	11.20±0.19	10.38±0.24	14.56±0.32	9.96±0.83	8.35±0.47
0.166	14.67±0.92	21.20±0.93	18.40±0.40	18.47±0.24	14.42±0.85	14.70±0.44
0.25	23.15±0.33	32.70±0.35	22.39±0.46	23.97±0.86	19.25±0.92	18.96±0.48
0.5	38.34±0.71	45.10±0.39	31.23±0.18	33.28±0.34	24.43±0.66	22.04±0.84
0.75	46.08±0.62	53.67±1.19	44.69±1.64	39.65±0.83	36.24±0.66	30.95±1.44
1	56.12±0.34	67.99±1.45	48.39±0.49	46.34±0.51	41.22±0.97	36.98±1.97
2	61.42±0.44	71.11±0.83	52.29±0.73	58.76±1.88	62.22±0.39	41.07±0.44
4	71.67±0.84	84.53±1.65	54.35±0.64	67.75±1.44	79.25±0.46	46.94±0.49
6	83.98±1.02	96.97±0.97	57.94±1.86	76.44±1.66	83.54±0.24	51.73±0.58
8	96.67±1.66		63.97±1.55	81.89±1.99	94.55±0.76	55.73±0.65
10			67.97±0.85	85.36±0.74		68.93±0.53
12			70.34±0.66	89.23±0.67		68.75±0.41

Fig.2:Comparative drug release profiles(F1-F6) at 240 nm

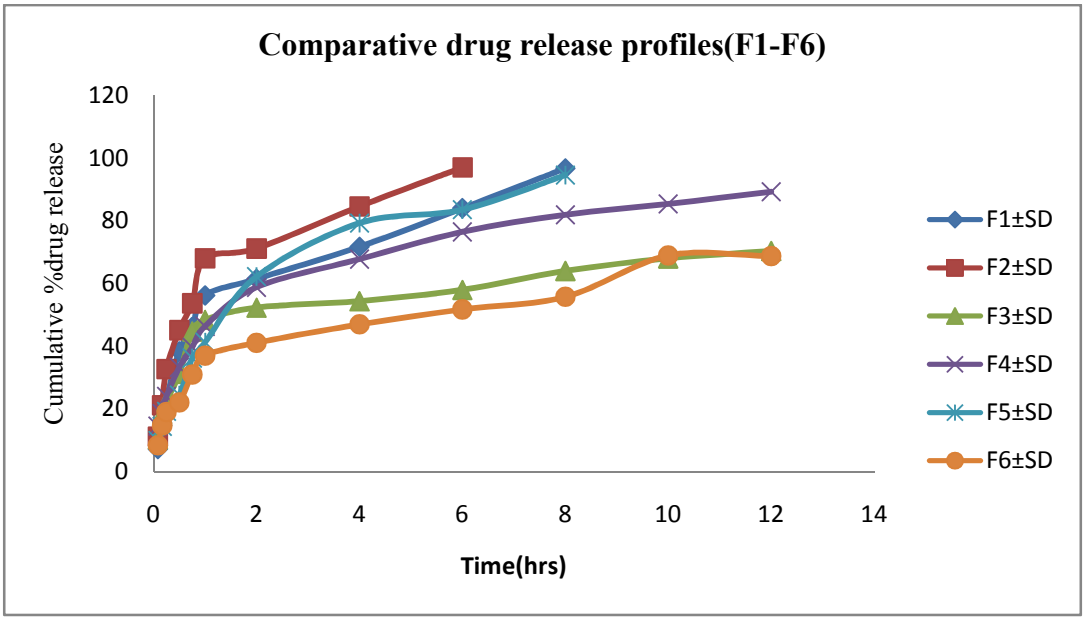


Table 11: Comparative drug release profiles(F7-F12) at 240 nm

Time(hrs)	F7±SD	F8±SD	F9±SD	F10±SD	F11±SD	F12±SD
0.083	9.46±1.54	9.69±1.74	5.87±0.31	4.15±0.39	5.82±0.48	8.45±0.35
0.166	14.88±0.33	13.31±1.30	11.28±0.74	11.01±0.29	10.53±0.74	12.74±0.82
0.25	26.84±0.94	21.29±0.84	23.90±0.64	18.25±0.15	16.45±0.82	16.95±0.53
0.5	37.94±0.27	22.14±0.63	26.98±0.39	22.35±0.21	27.49±0.62	23.64±0.98
0.75	41.05±0.94	30.57±0.91	31.90±0.67	31.34±0.99	36.83±0.86	25.21±0.42
1	46.14±0.29	42.14±0.55	35.99±0.16	37.20±0.89	44.39±0.72	25.08±0.66
2	54.93±0.37	55.42±0.86	39.79±058	41.84±0.28	57.75±0.43	27.66±0.73
4	64.73±0.96	66.09±0.28	41.00±0.58	45.96±0.36	66.71±0.29	31.28±0.42
6	70.33±0.53	77.47±0.61	46.29±0.76	51.44±0.97	72.31±0.39	32.31±0.79
8	76.12±0.41	84.94±0.82	52.20±1.37	59.14±0.37	81.62±0.37	37.20±0.43
10	79.94±0.23	98.25±0.54	54.35±1.19	61.80±0.74	87.06±0.92	41.44±0.98
12	80.09±0.76			58.68±1.18	96.40±0.83	47.42±0.56

Fig.3:Comparative drug release profiles(F7-F12) at 240 nm

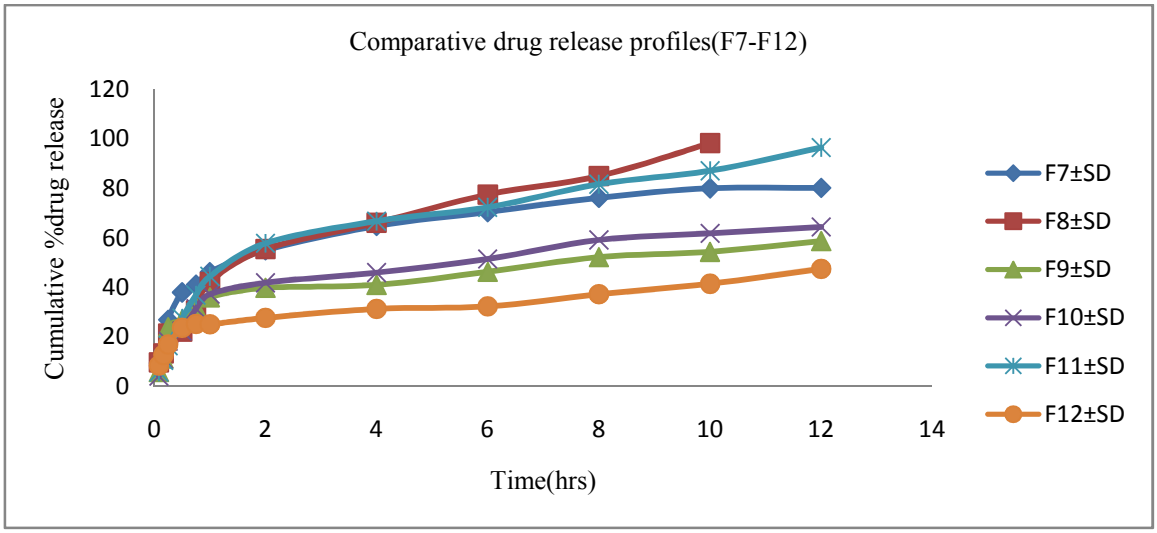


Table 12:Comparative drug release profiles(F13-F15) at 240 nm

Time(hrs)	F13±SD	F14±SD	F15±SD
0.083	11.33±0.29	12.56±0.73	18.93±1.42
0.166	15.43±0.84	19.78±0.45	24.62±1.92
0.25	21.42±0.65	26.52±0.76	35.04±1.92
0.5	28.62±0.54	31.62±0.53	37.09±0.63
0.75	35.42±0.67	37.85±0.76	48.62±0.83
1	45.57±0.43	42.74±0.99	53.09±0.94
2	58.73±0.86	51.92±0.64	67.95±1.76
4	62.47±0.53	54.84±0.98	71.03±1.91
6	67.28±0.44	70.56±0.39	82.42±0.04
8	70.08±0.77	74.54±0.85	95.58±0.93
10	75.47±0.84	77.42±0.93	
12	78.42±0.49	84.96±0.58	

Fig.4: Comparative drug release profiles(F13-F15) at 240 nm

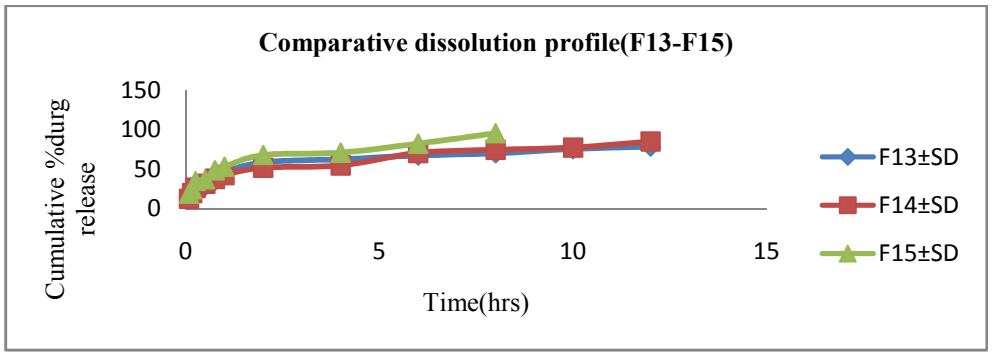
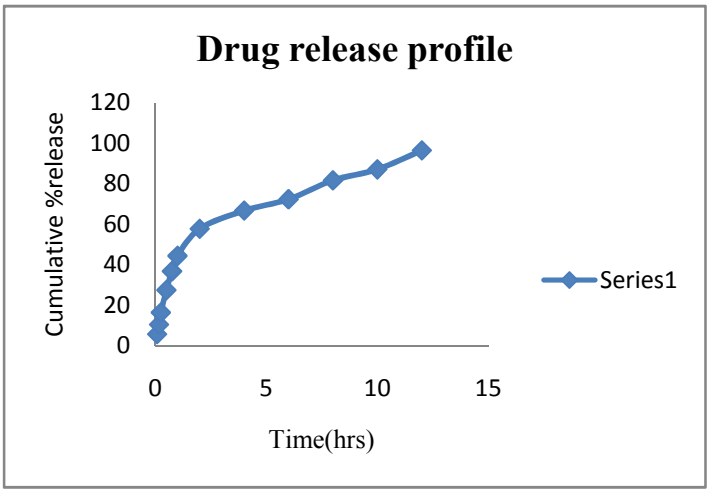


Table 13:Cumulative % release of formulation F11

Time (hrs)	F11 ± SD
0.083	5.82 ± 0.48
0.166	10.53 ± 0.74
0.25	16.45 ± 0.82
0.5	27.49 ± 0.62
0.75	36.83 ± 0.86
1	44.39 ± 0.72
2	57.75 ± 0.43
4	66.71 ± 0.29
6	72.31 ± 0.39
8	81.62 ± 0.37
10	87.06 ± 0.92
12	96.40 ± 0.83

Fig.5:Cumulative % release of formulation F11



Among all the formulations prepared (F1-F12), formulation F11 containing 60 % of xanthan gum displayed 95% drug release at 12 hours. This is because xanthan gum provides required tortuous and resistant barrier for the diffusion of drug molecules from matrices. Due to iteasy fabrication and less adverse effects associated xanthan gum was optimized as controlling release polymer for retarding the release rate of carvedilol.

Proportion of xanthan gum was increased from 10%-60%. It was found that below 10% xanthan gum might not give the sufficient strength to the matrix to control the drug release upto 12 hours, which indicates that at higher concentration (above 60%) xanthan gum further retards the release rate of the drug which is undesirable.

SUMMARY AND CONCLUSION

GFDDS of carvedilol were developed with natural (polymers) gums like guar gum, xanthan gum, okra gum to deliver carvedilol to the upper parts of the small intestine in a controlled manner to improve its bioavailability. Gastric floating drug delivery systems offer numerous advantages over other gastric retention systems. The effect of different formulation parameters and drug release kinetics were studied and the formulations were optimized. At lower concentration, gums acted as a rapid swelling agent and improved floating characteristics, but at higher concentrations decreased the compactness of the tablets due to its disintegrant action and also lag time the concentration of the gums was optimized to protect integrity of the tablet. The correlation coefficients and the slope values from Higuchi plots indicated that the release mechanism followed diffusion and erosion with zero order kinetics. From the results it can be concluded xanthan gum and sodium bicarbonate as gas generating agent provides the 96.40% of drug release up to 12hours.

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