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FORMULATION AND *IN-VITRO* EVALUATION OF CHEWABLE TABLETS OF CARVEDILOL

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ABSTRACT

The objective of the present research work is to develop a formulation of carvedilol chewable tablets. The carvedilol belongs to the class of beta-adrenergic blockers which is used in the treatment of congestive heart failure, chest pain and hypertension. These marketed tablets are taken by swallowing. In order to reduce this problem chewable tablets are more efficient. The chewable tablets are prepared by using sweetening agent is aspartame to mask the bitter taste of the drug. Carvedilol chewable tablets are prepared by wet granulation method. Chewable tablets were prepared and evaluated. The pre-formulation studies of FT-IR revealed that there was no significant interaction observed between the drug and excipients. Formulated chewable tablets were characterized for appearance, weight variation, hardness, friability, drug content, *in-vitro* drug release studies. Formulation F8 containing 30mg of Sodium starch glycolate released 99.38% drug at the end of 6th min better than other formulations. Formulation F8 could be considered as best formulation based on drug release profile, physical texture and other properties. Carvedilol chewable tablets could be served as promising drug delivery dosage form for cardiac patients with improved palatability and patients' acceptance due to pleasant taste of the formulation.

KEYWORDS

Chewable tablets, Carvedilol, Super disintegrating agents and Dissolution studies.

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INTRODUCTION

Administration of drugs through oral route is the most common and the easiest way to administer a drug. Chewable tablets have been designed so that they may be chewed in the mouth producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter a unpleasant taste. Chewable tablets are the dosage

forms, which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing of drugs. Chewable tablet includes palatability, stability, precise dosing, portability and ease of dosing. Chewable tablets have been designed so that they may be chewed in the mouth producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter a unpleasant taste. Chewable tablets are the dosage forms, which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing of drugs. Successfully tablet formulation development involves the careful selection of ingredients in order to manufacture a robust solid dosage form. Choosing the appropriate excipients to perform a specific function in a tablet formulation, such as disintegration or lubrication can be critical to achieving acceptable manufacturing performance. Sweeteners, both naturally occurring and synthetic, are one type of functional excipients commonly used in chewable tablet formulations to mask unpleasant tastes and facilitate paediatric dosing[1].

Chewable tablets are designed especially for the children and such persons who may have difficulty in swallowing the tablets. These are intended to be chewed in the mouth prior to swallowing and are not intended to be swallowed intact. Additionally, chewable tablets facilitate more rapid release and hence more rapid absorption of active ingredients and provide quick onset of action[2].

Chewable formulations are prepared in such a way that they can easily be crushed or smashed by chewing. They are usually formulated for patients who have difficulty in swallowing tablets. These classes of patients could also be adults with pathologically compromised throats or infants and youngsters who haven't learnt a way to properly swallow tablets with liquid. Chewable formulation also masks the bitter taste.

Carvedilol has been approved by FDA specifically to management of congestive heart failure commonly as a non-selective β- adrenergic receptors antagonist and an α-adrenergic receptor antagonist. Carvedilol reduces the risk of death, hospitalization and recuring heart attacks for patients with reduce heart functions following heart attacks and this is also used in treatment of hypertension and chest pain. It has a bitter taste with bioavailability of 25-35% following oral administration due to extensive first – pass metabolism. And biological half- life is about 6 hours. Carvedilol also available in the market in different formulation like tablets and capsules. Carvedilol sold under the brand name Coreg among others, is a medication used to treat high blood pressure.

Chewable formulations are widely acceptable dosage form and its most suitable for paediatric and geriatric patients. This type of formulations is designed to be processed by chewing which facilitate the release of active pharmaceutical ingredient. Advantages of chewable formulations are ease of manufacturing, long term stability, dosing accuracy, portability, it also facilitates swallowing as the product is initially broken down into particles in the oral cavity, since water is not required for their administration of the formulation, it has the benefit of convenience when dosing mostly in the case of paediatric and geriatric. Advantages of chewable tablets include the following (a) Ease of administration (b) Palatable *i.e.* it helps in masking the bitter taste of the formulation (c) should be of appropriate size and shape (d) rapid onset of action.

Chewable formulations include chewable tablets, medicating chewing gums, medicated jellies, lozenges, medicated lollipops and medicated chocolate formulation[3,4].

MATERIAL AND METHODS

Materials

Carvedilol, Maize starch, Sodium starch glycolate, Cross carmellose sodium, Cross-povidone, Lactose,

Aspartame, Citric acid, Magnesium stearate and Talc.

Methods

Determination of absorbance maxima (λmax) of carvedilol[5]

Accurately weigh 50mg of the Carvedilol drug and transfer it to 50ml standard volumetric flask and make up the volume using the acidic buffer pH 1.2 (stock solution). Further concentration was made 100µg/ml using the standard stock solution. From this 10µg/ml concentration was made using buffer. The dilution is kept in UV spectroscopy which is tested against the blank at 200-400nm and maximum absorbance was noted.

Preparation of calibration curve of Carvedilol[6]

Procedure for standard curve in acidic buffer pH 1.2: Weigh accurate quantity of 50mg of Carvedilol was dissolved in 50ml of pH 1.2 acidic buffer by shaking in volumetric flask 1000µg/ml (stock solution).From the above stock solution 2ml of solution was taken and made up to 50ml with pH 1.2 acidic buffer, which gives 40µg/ml concentration (sub stock solution). From the substock solution, concentrations of 4, 8, 12, 16, 20, 24, 28 and 32µg/ml in pH 1.2 acidic buffer was prepared. The absorbance of diluted solutions was measured at 285nm and a standard plot was drawn using the data with absorbance v/s concentration was plotted.

Preparation of carvedilol chewable tablets

Chewable tablets containing 6mg of carvedilol with total weight of tablet is 250mg by wet granulation method. All powder compounds were accurately weighed, passed through a standard sieve (sieve no 60) and blended uniform mixture. After being mixed powders were evaluated for bulk density and tapped density, compressibility index (Carr' index) and angle of repose. Chewable tablets were prepared by wet granulation method using rotary tablets compression machine with an average weight to 250mg were obtained. And hardness, friability, percentage weight variation, drug content, disintegration time and *in-vitro* drug release studies are carried out. Same procedure is carried out through nine batches.

Evaluation of Pre-compression parameters[7]

Angle of repose

In order to determine the flow property, the angle of repose was determined using the standard procedure. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane.

$\theta = \tan^{-1}(h/r)$

Determination of bulk density and tapped density

A quantity of 5gm of the powder (W) from each formula was introduced into a 25ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2sec intervals. The tapping was continued until no further change in volume was noted.

The bulk density and tapped density were calculated using the following formulae.

Bulk density = W / V_o Tapped density = W / Vf

Where, W = weight of the powder,

Vo = Initial volume, Vf=Final volume

Compressibility Index (Carr's Index) It was identified using the formula,

$C.I = 100(V0 - Vf)/ v$

Evaluation of Post compression parameters[8]

Shape of Tablets

The Compressed tablets were examined under the magnifying lens for the shape of the tablet.

Tablet Dimensions

Thickness and diameter were measured using acalibrated vernier caliper. Five tablets of each formulation were taken randomly and thickness was measured individually.

Hardness

Hardness indicates the ability of a tablet to with stand mechanical shocks while handling. The hardness of the tablet was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Five tablets were randomly picked and hardness of the tablet was determined.

Friability Test

The friability of tablets was determined using Rochefriabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (w0 initial)

and transferred into friabilator was operated at 25rpm for 4 mins or run up to 100 revolutions. The Tablets were weighed again (w). The friability was then calculated by Friability=100(1-w/w0).

Weight Variation Test

Twenty tablets were selected at random and the average weight was determined.

% Maximum positive deviation = (WH –A/ A) x 100

% Minimum negative deviation = (A-WL/ A) x100

Where, WH=Highest weight in mg, WL=Lowest weight in mg, A= Average weight of tablet.

Drug Content Estimation

Five tablets were weighed individually and powdered. The powder equivalent to average weight of the tablet was weighed and drug was extracted in 0.1(N) HCl pH 1.2, the drug content was determined measuring the absorbance at 285nm after suitable dilution using UV visible spectrophotometer[9].

Disintegration Test

Disintegration test was carried out by using disintegration test apparatus. One tablet is placed in each tube, and the basket rack was positioned in a 1ltr beaker of water, at 37°C ±2°C. A standard motor-driven device is used to move the basket. Assembly containing the tablets up and down through a distance of 5 to 6cm at a frequency of 28 to 32 cycles per mins. The time taken for the tablet to disintegrate completely was noted.

***In-vitro* drug release study**

In vitro drug release studies were performed to provide the amount of drug that is released at a definite time period. In these release studies for all formulations were carried out using tablet dissolution USP type II (paddle method). The dissolution media used was acidic buffer, pH 1.2 maintained at 37±0.5^{o}C and rotated 50rpm. Aliquots were withdrawn at different time intervals and the same volume of fresh medium was replaced to maintain sink conditions. The samples were analyzed against acidic buffer pH 1.2 as blank at λ max 285nm using UV spectroscopy[10].

The graph of percentage cumulative drug release Vs Time is plotted.

RESULTS AND DISCUSSION

Melting point of carvedilol

Melting point of carvedilol was determined by using capillary tube method and it was found to be 113± 1.10°C.

FTIR spectroscopy

The IR spectrum of the drug sample was recorded. Characteristic peaks were observed and compared with the standard spectra in the I.P. All characteristic speaks were matching with standard spectra.

Determination of absorption maxima (λ_{max}) of carvedilol by UV-Visible spectroscopy

The λ_{max} of Carvedilol in acidic buffer pH 1.2 was found to be 285nm as show in the Figure No.5.

Standard calibration cure

The standard calibration curve was constructed in the concentration range of 4-32µg/ml. The Beer's law was obeyed within the above concentration range. The regression equation obtained was y =co-efficient, y= 0.0276x+0.0282 with r^2 value equal to 0.9986.

***In-vitro* drug release study**

The percentage cumulative drug release of the formulation F1 to F9 are shown in the below Table No.7.

Table No.1: Formulation of Carvedilol chewable tablet

S.No	Ingredients (mg)	Composition of different formulations of chewable tablets								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Carvedilol	6	6	6	6	6	6	6	6	6
2	Cross carmellose sodium	10	----	----	20	-----	-----	30	------	------
3	Sodium starch glycolate	-----	10	-----	----	20	-----	------	30	------
4	Cross povidone	-----	------	10	-----	-----	20	----	----	30
5	Aspartame	2	2	2	2	2	2	2	2	2
6	Citric acid	5	5	5	5	5	5	5	5	5
7	Magnesium stearate	3	3	3	3	3	3	3	3	3
8	Talc	3	3	3	3	3	3	3	3	3
9	Maize starch	75	75	75	75	75	75	75	75	75
10	lactose	146	146	146	136	136	136	126	126	126
11	Total	250	250	250	250	250	250	250	250	250

Table No.2: Dissolution studies condition

S.No	Apparatus	USPII apparatus
1	Dissolution medium	400ml of pH 1.2 HCl buffer
2	Temperature	37±0.5^{o}C
3	Rotating speed of the paddle	50rpm
4	Sampling Volume	5ml
5	Sample time intervals	2, 4, 6, 8, 10, 12, 14, 16, 18, 20 min
6	Detection	UV-Visible spectroscopy
7	Wavelength	285nm

Table No.3: FTIR Data

S.No	Name of the compound	Range in cm^{-1} (literature value)	Peaks in cm^{-1} (obtained value)	Functional group
1	Carvedilol	3300-3500cm^{-1}	3338.93cm^{-1}	Amines
		1080-1300cm^{-1}	1092.09cm^{-1}	C-O
		1080-1300cm^{-1}	1250.92cm^{-1}	Alcohols
2	Carvedilol + Croscarmellose sodium	3200-3600cm^{-1}	3254cm^{-1}	Hydroxyl group
		3300-3500cm^{-1}	3336cm^{-1}	Amines
		2850-2960cm^{-1}	2919cm^{-1}	Cyclic alkanes
3	Carvedilol+ crospovidone	2500-3000cm^{-1}	2924cm^{-1}	Carboxylic group
		3200-3600cm^{-1}	3339cm^{-1}	Free hydroxyl Group
		3200-3600cm^{-1}	3401cm^{-1}	Free hydroxyl Group
4	Carvedilol + Sodium starch glycolate	3300-3500cm^{-1}	3338.06cm^{-1}	Amines
		1270-1230cm^{-1}	1250.52cm^{-1}	OCH3
		1650-1580cm^{-1}	1594.20cm^{-1}	N-H
		1050-1000cm^{-1}	1007.90cm^{-1}	Hydroxyl group
		1080-1300cm^{-1}	1089.73cm^{-1}	Alcohol group

Table No.4: Evaluation of the pre formulation studies

Formulation Code	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Angle of repose (θ)
F1	0.41±0.04	0.44±0.02	13.29±1.43	27.67±0.31
F2	0.47±0.01	0.46±0.01	9.46±0.76	27.28±0.72
F3	0.49±0.04	0.52±0.03	13.72±0.36	25.65±1.26
F4	0.44±0.09	0.44±0.01	10.33±0.59	27.56±0.52
F5	0.45±0.03	0.45±0.05	15.51±1.35	26.41±1.28
F6	0.42±0.07	0.47±0.07	12.16±0.29	27.93±0.44
F7	0.44±0.01	0.41±0.08	15.61±1.32	26.30±1.45
F8	0.51±0.04	0.50±0.02	11.30±0.46	26.32±0.56
F9	0.49±0.05	0.51±0.05	10.25±1.37	27.54±1.11

Table No.5: Evaluation of the prepared formulation

Formulation code	Hardness (Kg/cm^2)	% Weight variation
F1	6.22±0.32	249.62±0.17
F2	5.93±0.18	249.66±0.19
F3	6.53±0.15	249.61±0.11
F4	6.46±0.26	249.72±0.12
F5	5.81±0.41	249.69±0.15
F6	6.37±0.22	249.59±0.19
F7	5.62±0.61	249.71±0.15
F8	5.13±0.31	249.64±0.21
F9	6.57±0.45	249.68±0.14

Table No.6: Disintegration time and drug content

Formulation Code	Disintegration time (in sec)	Drug content of Carvedilol (%)
F1	120±0.02	98.11
F2	115±0.05	96.24
F3	125±0.07	97.66
F4	93±0.01	97.12
F5	87±0.08	98.78
F6	95±0.05	95.34
F7	85±0.05	97.56
F8	78±0.07	98.43
F9	89±0.03	97.86

Table No.7: Maximum Percentage drug release of nine formulations (F1 to F9) at their respective time

Formulation code	Time (min)	%CDR
F1	14	96.23
F2	12	98.56
F3	14	94.60
F4	12	97.73
F5	10	96.15
F6	12	95.37
F7	10	98.52
F8	6	99.38
F9	8	99.26

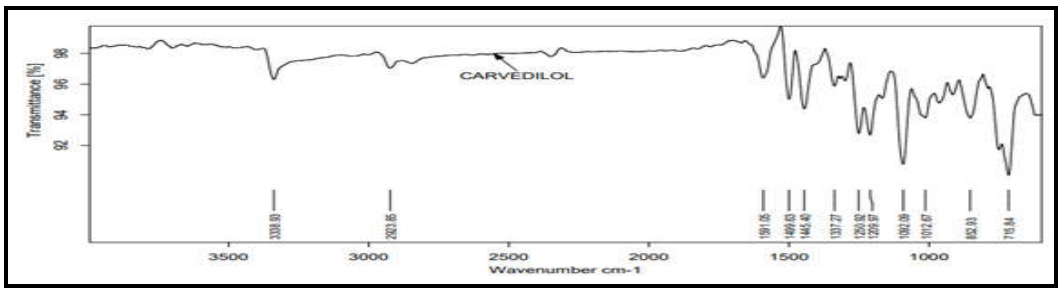

Figure No.1: FTIR of carvedilol

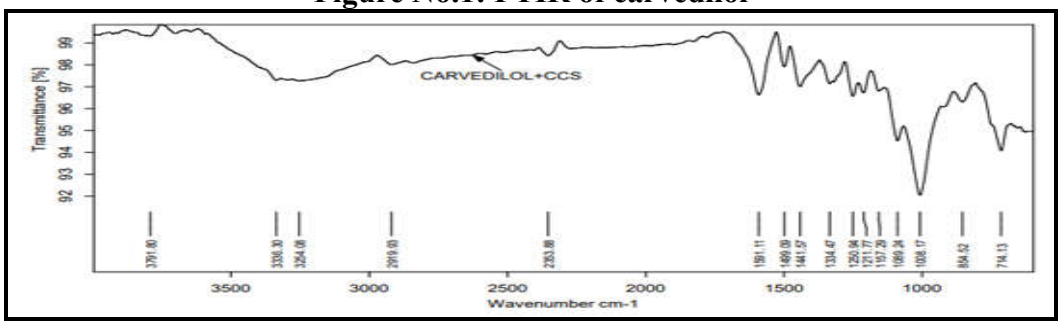

Figure No.2: FTIR spectra physical mixture of carvedilol and Croscarmellose sodium

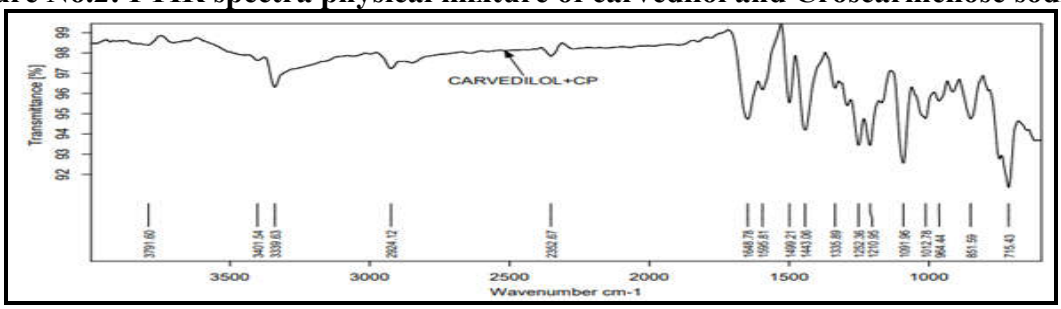

Figure No.3: FTIR spectra physical mixture of carvedilol and crospovidon

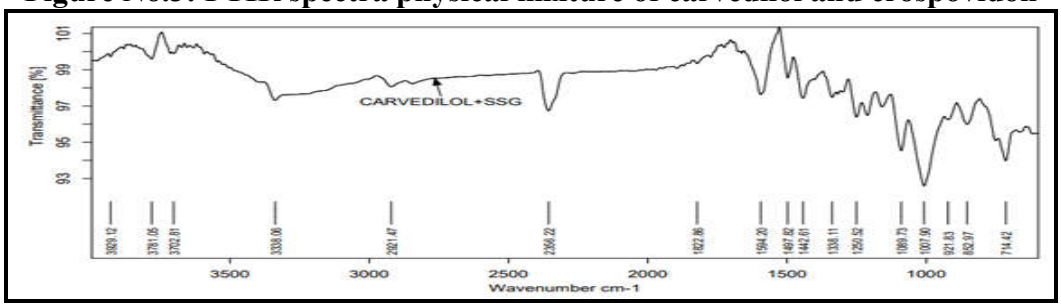

Figure No.4: FTIR spectra Carvedilol and Sodium starch glycolate

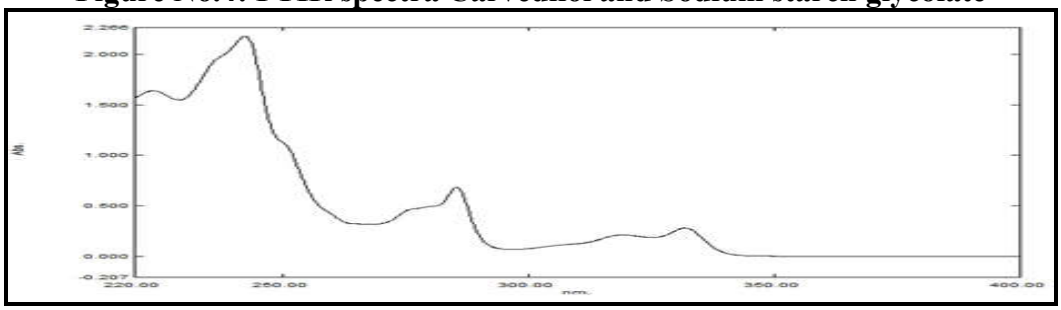

Figure No.5: Absorption maxima of carvedilol

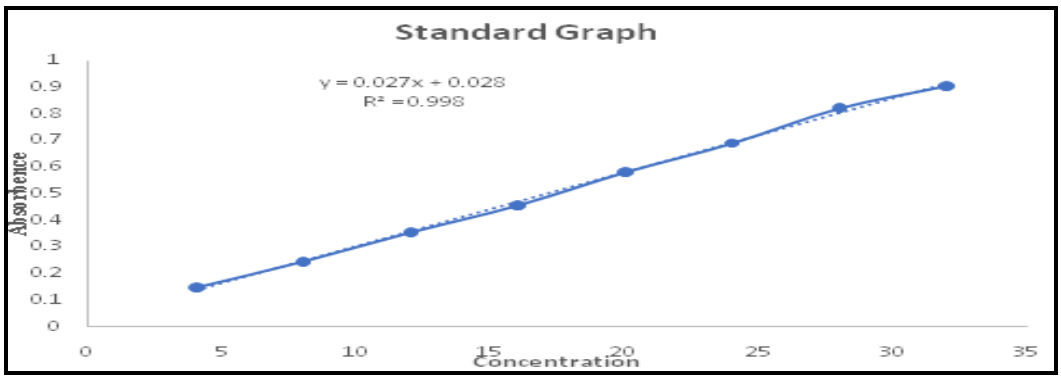

Figure No.6: Standard calibration curve of carvedilol

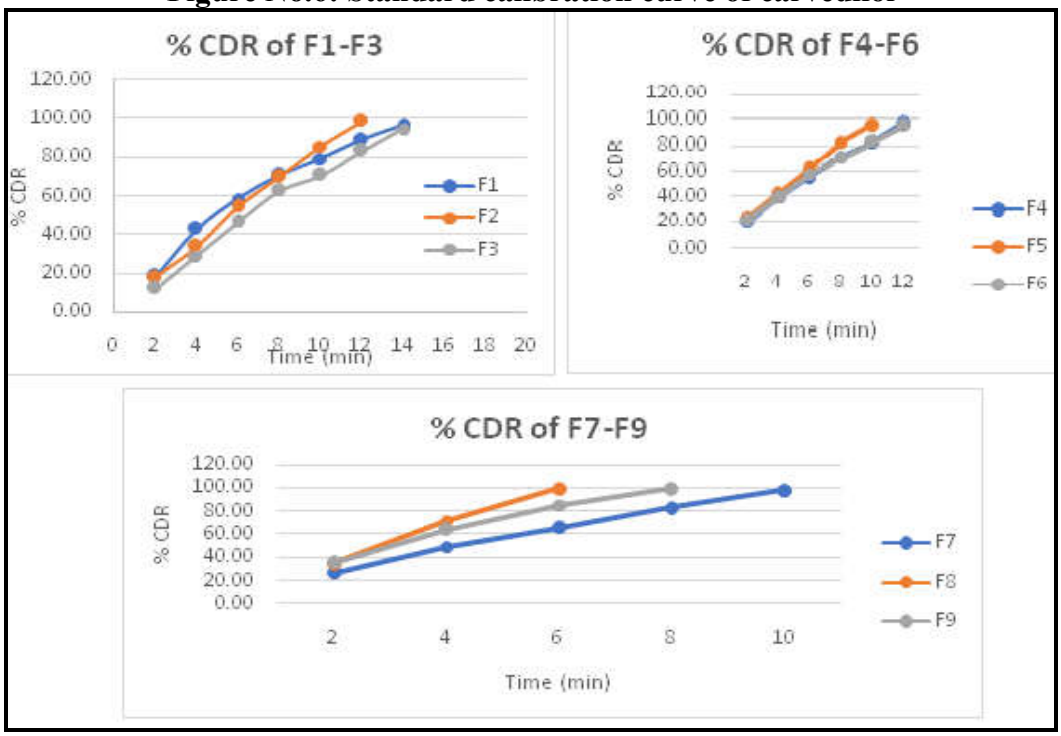

Figure No.7: Plot of % Cumulative drug release v/s time (min) of F1-F9

CONCLUSION

The present study is aimed to develop carvedilol chewable tablets with the sweeting agent to mask the bitter taste of the drug for treatment of congestive heart failure, chest pain and hypertension.

The pre-formulation studies were carried out. The drug sample was characterized for its physiochemical properties such as melting point, absorption maxima and FTIR studies. FTIR studies confirmed that there was no interaction between the drug and excipient, hence the selected excipient was found to be compatible with the drug.

Total nine different formulations of carvedilol tablet were formulated in using different excipients. The weight variation test, hardness and friability of the chewable tablets were within the standard limits. The drug content of the chewable tablets is within the pharmacopeial limits.

The *in-vitro* dissolution studies of all the nine formulations were carried out in the acidic buffer pH 1.2 for the 2 min time intervals.

Formulation F8 containing compound sodium starch glycolate have better drug release at the end of 6 min (99.38%) compared to the nine formulations. From the present studies it could be concluded that formulation F8 was the best formulation in terms of weight variation, hardness, friability, disintegration time, drug content and *in-vitro* drug release (99.38%).

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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