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FORMULATION AND EVALUATION OF FLOATING SUSTAINED RELEASE TABLETS

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Abstract:

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and Mechanical properties of drug substances in order to develop stable, safe and effective dosage forms. The following Preformulation studies were performed:

- ✓ Study of organoleptic properties
- ✓ Identification of Pure drug by UV Spectra ,IR spectrum
- ✓ Solubility analysis
- ✓ Melting point of drug
- ✓ Drug powder characterization

Key words: floating sustained release**,** Preformulation, Carvedilol.

Introduction:

The oral route is considered as the most promising route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day. This results in a significant fluctuation in drug levels. Recently, several technical advancements have led to the development of several novel drug delivery systems (NDDS) that could revolutionize methods of medication and provide several therapeutic benefits.[1]

In recent years scientific and technological advancements have been made in the research and development of oral controlled/sustained drug delivery systems to counter drawbacks of conventional drug delivery systems.[2] The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration due to the systematic drug delivery of drug via various pharmaceutical products of different dosage forms.[3]

ADVANTAGES: [4]

The oral route presents a convenient and safe way of drug administration. Compared to liquid dosage forms, oral dosage forms have general advantages in terms of the chemical and physical stability of the dosage form.[5,6] Oral dosage forms are convenient to handle and can be prepared in a versatile way with respect to their use and delivery of the drug. The preparation procedure enables accurate dosing of the drug. Oral dosage forms can be relatively and cheaply mass produced with robust and quality-controlled production.[7]

DISADVANTAGES: [4]

The onset of action of drug is late and hence is not fat. Therefore, oral route of administration is not preferred in emergency. As it is absorbed rom gastrointestinal tract, the quantity if doses of drug required is more.

- It is difficult route of administration of drug for non-cooperative patients like babies and children.
- It is also difficult route of administration of drug for unconsciousness patients.
- The absorption of drug from gastrointestinal disorders like acidity, loss of appetite, etc.
- The uncertainty of maintenance of the prescribed dosage of drug is possible in oral route of administration.
- Drug may be destroyed or inactivated by the enzyme in gastrointestinal tract.

1.2 Concept of absorption window: [8]

Drug exhibiting absorption from only a particular portion of GI tract or showing difference in absorption from various regions of GI tract are said to have regional variability in intestinal absorption. Such drugs show absorption window which signifies the regions of GI tract from where absorption primarily occurs. Drug released from the CRDDS after the absorption window has been crossed goes waste with no or negligible

absorption (Figure 1). This phenomenon drastically decreasesthe available drug for absorption, after release of drug from CRDDS. The CRDDS possessing the ability of being retained in the stomach are called GRDDS and they can help in optimizing the oral controlled delivery of drugs having absorption window by continuously releasing drug prior to absorption window, for prolonged period of time thus ensuring optimal bioavailability.

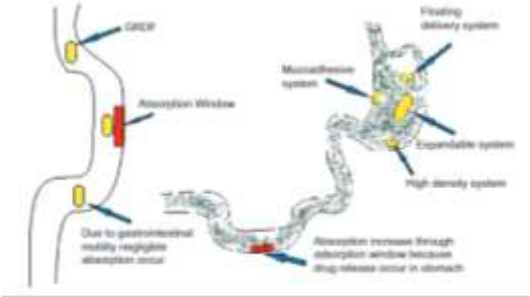


Figure No. 1: Drug absorption in the case of conventional dosage forms (A) and principles of GRDF (B)

GASTRORETENTIVE DRUG DELIVERY SYSTEM

GRDDS is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bio adhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, super porous hydrogel systems, magnetic systems etc.[9]

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.[10] It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[11]

- The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physicochemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH of the gastro-intestinal tract (GIT) and so on. Conventional dosage forms reside in stomach and intestine for only short period. So, there is a need of dosage form that increases residence time of drugs in absorption site.
- The aim of the present work is to formulate gastric floating tablets of Carvedilol and to prolong the gastric residence time of active drug moiety there by maximizing absorption and bioavailability by using Swellable polymers like Sodium CMC, sodium Alginate and Guar gum.
- Carvedilol is a α1, β1 & β2 adrenergic antagonist. It is currently indicated for management of mild-to-moderate essential hypertension. Carvedilol is selected as a model drug for this investigation because maximum dose daily 25mg twice daily, short biological half-life(7-10hrs) and poor bioavailability(25-30%) due to extensive hepatic first pass metabolism in the liver.
- As Carvedilol has higher absorption in the proximal region of the GI tract and poor absorption and degradation in colon, suggest it is an ideal candidate for a gastroretentive drug-delivery system that will

prolong the gastric residence time of the dosage form.

- So, planned to formulate and evaluate floating sustained release tablets of Carvedilol by using different polymers.
- One of the purposes of this formulation was to maintain in vitro buoyancy as well as duration of floating stable for at least 12 hours and sustained drug release in *invitro* dissolution study.
- Rate of drug release and mechanism of drug release from the designed tablets were evaluated.

Materials and Methodology

The materials required for development of Gastroretentive tablet of Carvedilol.

LIST OF MATERIALS

Table no. 1: List of excipients used in formulation development and study.

S.NO	MATERIAL	PROPERTY	SUPPLIED/PURCHASED
	Carvedilol	Pure drug	SUN PHARMA gift sample
	Guar gum	Polymer	Loba chemie pvt. Ltd, Mumbai
	Sodium- CMC	Polymer	Rolex chemical industries, Mumbai
	Sodium alginate	Polymer	Thomas baker chemicals Pvt ltd, Mumbai
	Sodium bicarbonate	Gas generating agent	Nice chemicals, Kerala
	Citric acid	Gas generating agent	s. d. fine-Chem Ltd, Mumbai
	MCC	Bulking agent and diluent	s. d. fine-Chem Ltd, Mumbai
	Magnesium stearate	Lubricant	Loba chemie pvt. Ltd, Mumbai
	Potassium chloride	Buffer salt	Spectrum reagents and chemicals Pvt. Ltd, Kerala
	Methanol	Solvent	Nice chemicals, Kerala
	Ethanol	solvent	Nice chemicals, Kerala

LIST OF INSTRUMENTS

Table No.2: List of Equipment and their manufacturer

S.NO	EQUIPMENTS/INSTRUMENTS	SOURCES
	Digital weighing balance	Global factory network, India.
	Cary 630 FTIR spectrophotometer	Agilent Cary 630 FTIR.
	UV-visible spectrophotometer	Shimadzu-UV- 1800, Japan
	Melting point apparatus	Deen instrument, India
	Rotary Tablet Press – 12 Station	Rimek Mini Press-fl MT, Gujarat
	Dissolution Tester (USP)	Electro lab TDT-081, India
	pH meter	El ico L 1 120. India.
	Friability Test Apparatus	LAB-HOSP. Mumbai
	Pfizer Tablet Hardness Tester	Scientific Engineering Corporation. India
	Vernier caliper	Besto, India

PREFORMULATION STUDIES:

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and Mechanical properties of drug substances in order to develop stable, safe and effective dosage forms. The following Preformulation studies were performed:

- ✓ Study of organoleptic properties
- ✓ Identification of Pure drug by UV Spectra ,IR spectrum
- ✓ Solubility analysis

- ✓ Melting point of drug
- ✓ Drug powder characterization
- ✓ Drug-excipients compatibility study **PREFORMULATION STUDIES:**The following Preformulation studies were performed: Study of organoleptic properties
- ✓ Identification of Pure drug by U.V Spectra ,IR spectrum
- ✓ Solubility analysis
- ✓ Melting point of drug
- ✓ Drug powder characterization
- ✓ Drug-excipients compatibility study

Study of organoleptic properties: These tests were performed as per procedure according to the I.P. The drug sample was found to be white powder and non-sticky.

Table NO 3: Observation for organoleptic properties:

TEST	SPECIFICATION	OBSERVATION
Colour	A White or almost white, Crystalline powder	A White crystalline powder
Odour	---	Odourless

Identification of Pure drug by U.V Spectra ,IR spectrum

UV Spectra of Carvedilol:-

The λ max of Carvedilol was found to be 240 nm and reported λ max of Carvedilol was also 240 nm. It indicates that procured Carvedilol complies the I.P limits for UV spectrum.

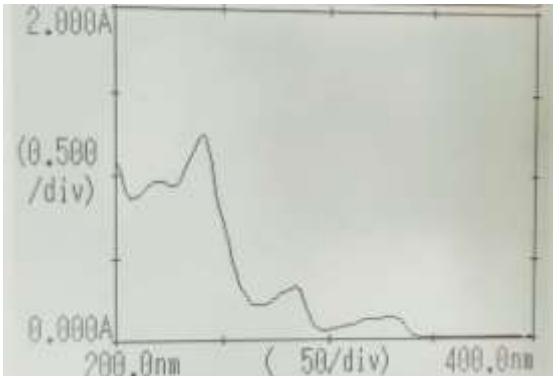


Figure No. 2:- Observed UV spectra of an Carvedilol [56]

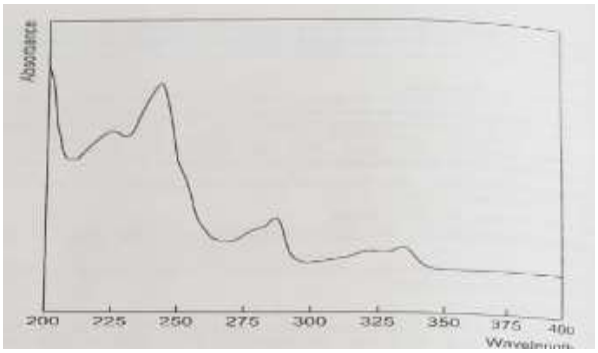


Figure No. 3:- Standard UV spectra of a Carvedilol [56]

Infrared spectrum of drug:-

The Fourier transform infrared spectroscopy (FTIR) spectrum of Carvedilol using which % T verses wave

Number was studied.

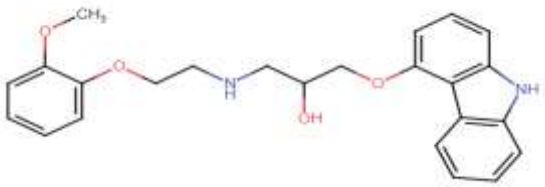


Fig. No: 4 Chemical Structure of Carvedilol

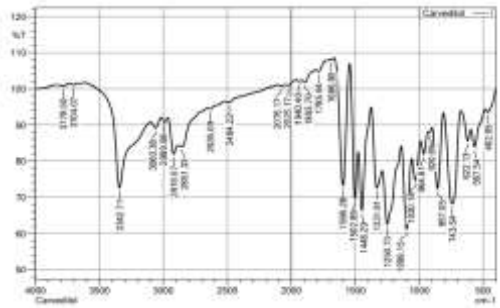


Figure No 5 :- IR Spectra of a Carvedilol

Table 4:- IR peaks of Carvedilol.

S.NO	FUNCTIONAL GROUP	ACTUAL VALUES CM^{-1}	VALUES OBTAINED
1.	**N-H** Streching	3500 – 3100	3342.71
2.	**O-H** Streching	3400 – 2400	2989.98
3.	**C-H** Streching	3000 – 2850	2919.57
4.	**C-O** Streching	1300 – 1000	1250.73
5.	**C=C** Aromatic	1600 – 1450	1502.89
6.	**C-N** Streching	1350 – 1000	1099.15
7.	**N-H** stretching in chain	1550 – 1640	1596.28
8.	**C=CH$_2$** Bending	≈ 900	920.99

6.3 Solubility analysis:

Carvedilol samples are examined and it was found to be insoluble in water and slightly soluble in methanol. It also dissolved indilute alkali and in dilute acids.

6.4 Melting point of drug:

The melting point of carvedilol was determined by capillary method, meltingpoint of carvedilol was found to be 115.3±1.52 °C. Melting point compared with USP standards that showed that drug is pure.

Table No. 5 : observation for Melting Point

Test	Loss on drying	Observation			Mean (SD)
		1	2	3	
Melting point	114-119^{0}C	115	114	116	115.3±1.52

6.5 Loss on Drying:

Table 6: **Observations for loss on drying**

Test	Loss on drying	Observation
Loss on drying	Not more than0.5% w/w	0.19% w/w

The loss drying of drug was found as 0.19% w/w which is within the limit of I.P.

6.6 Drug powder characterization:

Angle of repose:

It was determined as per procedure. The results were given in table no. 15

Table-7: Angle of repose for drug

Material	Angle of repose
carvedilol Raw material	28.96

The results indicate according to the limits of pharmacopeia that the raw material has good flow property.

Flow properties:

It was determined as per procedure. The results were given in table no. 16.

Table-8: Flow properties of pure drug

Material	Bulk density	Tappeddensity	Carr's index (%)	Hausner ratio(%)
carvedilol rawmaterial	0.35	0.16 gm/ml	11	1.112

The results clearly indicate that the carvedilol raw material has good flowproperty according to the limits of the standard.

6.7Drug Powder Characterization:

Table No 9: 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	27.17±0.01	0.377±0.03	0.61±0.04	15.21±0.07	1.05±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-polymer compatibility study:

FTIR studies:

The FTIR spectra of the pure drug, excipient and physical mixture of drug and excipients used in floating tablet formulations shown in Fig no 14-17 were recorded in between 400-4000 wave number (cm^{-1})

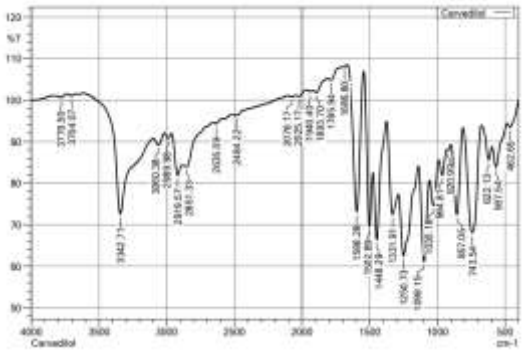


Figure No. 6 : FTIR spectrum of carvedilol standard

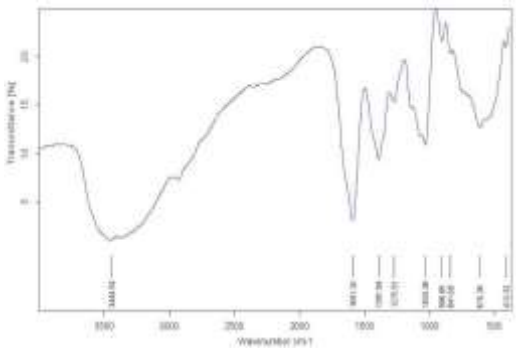


Figure No.. No 7 :FTIR Spectrum of carvedilol, polymers, and excipients (Physical Mixture 1)

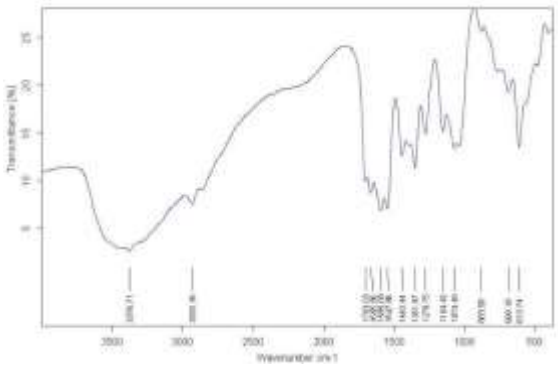


Figure No:8 : FTIR Spectrum of carvedilol, polymers and excipients (Physical Mixture 2)

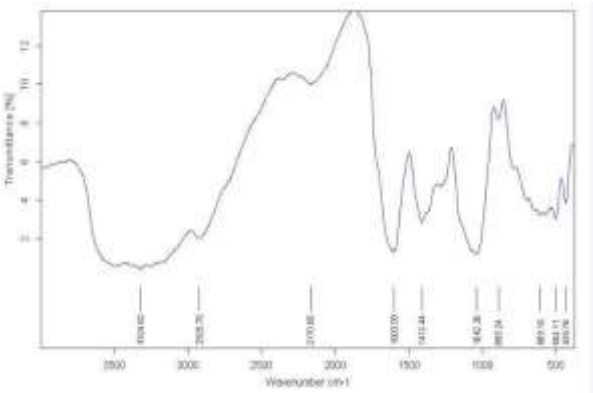


Figure No9 : FTIR Spectrum of carvedilol, polymers, and excipients (Physical Mixture 3)

Table : 10: FT-IR Peaks of drug and physical mixtures

S.No	FUNCTIONAL GROUP	Peak in puredrug (cm^{-1})	Peak in Physical Mixture		
			1	2	3
1.	**N-H** Streching	3342.71	3344.12	3344.12	3342.48
2.	**O-H** Streching	2989.98	2957.905	2997.18	2997.18
3.	**C-H** Streching	2919.57	2916.99	2918.62	2916.99
4.	**C-O** Streching	1250.73	1251.02	1251.02	1251.02
5.	**C=C** Aromatic	1502.89	1501.407	1501.407	1501.407
6.	**C-N** Streching	1099.15	1100.46	1098.82	1095.55
7.	**N-H** stretching in chain	1596.28	1586.506	1588.14	1586.506
8.	**C=CH₂** Bending	920.99	850.07	850.07	869.71

6.9 Differential scanning calorimetry (DSC):-

The DSC curves of pure Carvedilol and powdered formulation F9 containing Carvedilol along with the polymers (Sodium CMC) and excipients (MCC, Sodium bicarbonate, citric acid, and magnesium stearate) used in Optimised Formulation F9.

Carvedilol showed a characteristic sharp endothermic peak at 116.17^{0}C, indicating the melting point of the drug. The obtained DSC curve for formulation F9 shows the endothermic peak at 116.17 ^{0} C of Carvedilol. The endothermic peak of drug slightly shifted to lower temperature i.e., 116.17^{0}C to 113.39^0 C due to the presence of magnesium stearate.

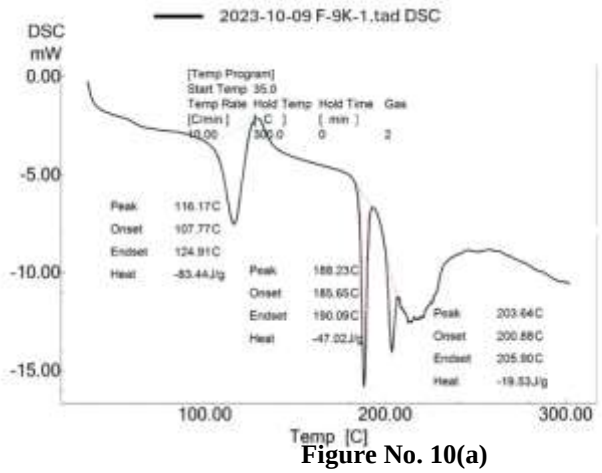
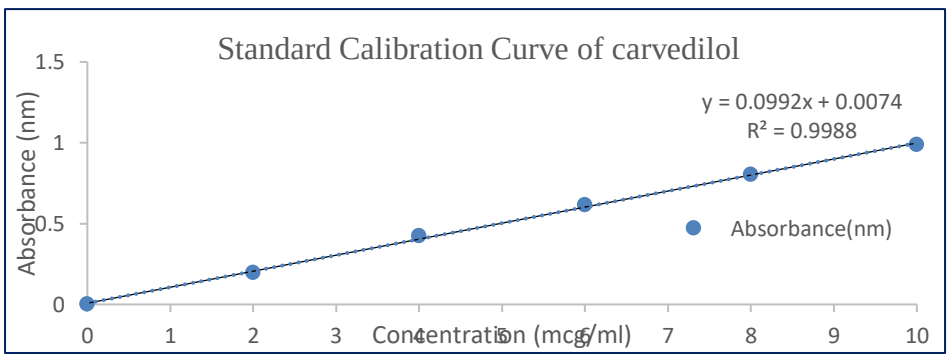


Figure No. 10(a)

Figure No. 10: a. DSC thermogram of pure Carvedilol. b .DSC thermogram of formulation F9 after stability studies.



6.10 STANDARD CURVE OF CARVEDILOL PURE DRUG:

Calibration curve of carvedilol was determined by plotting absorbance (nm) versus concentration (µg/ml) at 240 nm. The results were obtained as follows.

Table -:11 Calibration report of Carvedilol

S.No	Concentration (µg/ml)	Absorbances at 240nm
1	0	*0*
2	2	*0.19*
3	4	*0.42*
4	6	*0.62*
5	8	*0.82*
6	10	*0.95*

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

Figure No. No.11 : standard plot for Carvedilol in 0.1 N HCL

1 Pre-Formulation Studies:

The identification of pure drug carvedilol was carried out as per IP and confirmed that the sample is authenticated. The UV spectra, IR spectra and melting point analysis of the drug match with the standard values. The loss on drying of drug was found to be 0.19% which is within the limits of B.P. Carvedilol is found to be insoluble in water and slightly soluble in methanol. It also dissolved indilute alkali and in dilute acids. The results were found to be similar when compared to Standard I.P.

7.2 Drug Polymer Compatibility Studies Using FT-IR

To investigate the possible chemical interaction between drug and selected polymers, FTIR studies were carried out. IR spectrum for pure drug and physical mixture of drug- polymers were obtained and analyzed for principle peaks at 3342.71 cm^{-1} due to the **N-H** Streching, 2989.98 cm^{-1} due to **O-H** Streching, 2919.57cm^{-1} which is Characteristic to **C-H** Streching, 1250.73 cm^{-1} due to **C-O** group, 1502.89 cm^{-1} characteristic to Aromatic **C=C** Stretch and 1099.15 cm^{-1} characteristic to **C-N** Streching, 1596.28 cm^{-1} which is due to **N-H** stretching in chain, 920.99 cm^{-1} characteristic to **C=CH₂** Bending. The FTIR characteristic of carvedilol peak results were found to be similar to the I.P. standard carvedilol peaks. The FTIR characteristic of Carvedilol with polymers resembles almost with the spectra of authentic sample of Carvedilol. The studies suggest that there is no incompatibility between drug and polymer.

7.3 Drug polymer compatibility studies using DSC

To investigate the possible physical interaction between drug and excipients, DSC studies were carried out. Pure drug showed sharp endothermic peak at 116.17^0C, indicating the melting point of the drug. The sharp endothermic peak of sample carvedilol was nearly to the standard peak of carvedilol according to the USP monographs. The optimised formulation F9 is taken and the thermal behavior of sample is determined using differential scanning calorimeter, endothermic peak obtained is at 113.39^0 C. No significant change in

the endotherm of the drug was observed in optimised floating tablets. From this it was inferred that there was no interaction between the drug and excipients.

7.4 Powder Flow Properties

The results of Pre-formulation parameters for formulated physical mixtures of all batches. The flowability of the polymers was found to be good according to the limits of I.P.

7.5 Lambda max of drug: UV- Spectra of pure Carvedilol was taken as per the procedure described in I.P. The absorption maxima of pure drug carvedilol were scanned in range of 200-400 cm^{-1}. The maximum λ max recorded 240 nm. The resulted absorption maxima were found to be nearly to the reported peak of carvedilol in I.P.

Construction of Standard Calibration Curve for Carvedilol

Calibration curves of carvedilol in 0.1N HCL buffer pH 1.2 solutions were built at λ max recorded 240 nm. Beer's law followed to construct the calibration curve was in the concentration range of 2-10 µg/ml. The standard graph of carvedilol was plotted according to the procedure, and its linearity appears. The standard graph of carvedilol demonstrated great linearity with an R^2 of 0.998, which indicates that it complies "Beer-Lambert's" law.

Formulation development:

Gastric Floating tablets of Carvedilol were prepared by direct compression using the Microcrystalline cellulose, in alone and in combinations as rate controlling polymers, Sodium alginate, guar gum, Sodium CMC, as binder, citric acid and Sodium bicarbonate as Gas generating agents, Magnesium stearate as glidants.

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