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FORMULATION, DEVELOPMENTAND EVALUATION OF EXTENDED-RELEASE TABLET OF CARVEDILOL PHOSPHATE

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ABSTRACT

The oral route is the most popular route due to ease of administration and to the fact that gastrointestinal physiology offers more flexibility. The matrix system is one of the intricate approaches for the preparation of the sustained release dosage forms and formulation of matrix tablet has gained immense popularity now a day because it has the advantage of simple processing and low cost of fabrication. Formulated oral sustained release matrix tablets of Carvedilol Phosphate in order to improve efficacy, reduce the frequency of administration, and better patient compliance. Matrix tablet of Carvedilol Phosphate, prepared using Sodium carboxymethyl cellulose and HPMC K4M can successfully be employed in oral controlled release drug delivery system, as it is likely to increase its GI residence time, and eventually, improve the extent of bioavailability. However, appropriate balancing between various levels of the two polymers is imperative to acquire proper controlled release. The physicochemical compatibility of the drug with polymers was established through FTIR spectroscopy. All blended formulations were evaluated for bulk density, tapped density, Carr's index, angle of repose and the Hausner's ratio. All these results indicated that, the powder blend showed good flow properties. All tablet formulation has their weight within 498 to 501 mg and were uniform in diameter. The formulation batch F1 and batch F9, all trials have the sufficient hardness and friability i.e., with in the limit. In dissolution studies formulation F7 given best drug release up to the 24 hrs compared to other formulation and it follows zero order kinetics. Accelerated stability studies results were found within limits.. Extended release tablet of Carvedilol Phosphate can be successfully employed to treat hypertension and congestive heart failure condition.

KEYWORDS: Zero order kinetics, Higuchi model, Korseymey-peppas model, Carvedilol Phosphate, Sodium CMC and HPMC K4M.

1. INTRODUCTION

There are several reasons for attractiveness of these dosage forms provides increased bioavailability of drug product, reduction in frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak through concentration and side effect and possibly improves the specific distribution of the drug. If one were to develop an ideal drug delivery system, two pre- requisites would be required. Firstly single dose for the duration of treatment whether for days or weeks as with infection, diabetes and hypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects. There is certain consideration for the preparation of extended release formulation. If the active compound has a long half-life, it is sustained on its own, If the pharmacological activity of the active compound is not directly related to its blood levels, If the absorption of the drug involves an active transport and If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors need serious review prior to design.[1-6]

In the 1980s, FDA introduced rigorous regulations governing bioequivalence and *in vitro–in vivo* correlations for controlled-release products. Required pharmacokinetic evaluations involve.

- Relative bioavailability following multiple dose.
- Dose proportionality.
- Unit dosage strength proportionality.
- Single-dose bioequivalence study (experimental versus marketed formulations at various strengths).
- Pharmacokinetic/ Pharmacodynamic (PK/PD) relationship.
- *In vivo-in vitro* correlation (IVIVC).

Advantages of Extended Release Delivery System[7-9]

Extended release products have many advantages.

1. The extended release formulation reduces dosing frequency of drugs.
2. The extended release formulation may maintain therapeutic concentrations.
3. Reduce the toxicity by slowing drug absorption.
4. The use of these formulations avoided the high blood concentration.
5. Extended release formulation has the potential to improve the patient compliance and convenience.

6. Minimize the local and systemic side effects.
7. Increase the stability by protecting the drug from hydrolysis or other degradation changes in gastrointestinal tract.
8. Improvement in treatment efficacy.
9. Minimize drug accumulation with chronic dosing.
10. Improve the bioavailability of some drugs.
11. Usage of less total drug.
12. Improve the ability to provide special effects.

For example: Morning relief of arthritis through bed time dosing.

Disadvantages of extended release delivery system[7- 9]

1. Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
2. The larger size of extended release products may cause difficulties in ingestion or transit through gut.
3. The release rates are affected by various factors such as food and the rate of transit through the gut.
4. Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
5. High cost of preparation.
6. Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.
7. Unpredictable and poor *in vivo* and *in vitro* relationship.
8. Effective drug release time is influenced and limited by GI residence time.
9. Need additional patient education.
10. Drug having very shorts half-life and very long half-life are poor candidates for extended release dosage form e.g. Diazepam.

Drawbacks of conventional dosage forms

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index (TI) whenever over Medications occur.

Matrix drug delivery system[10-15, 17]

In matrix systems a polymer: drug solution or dispersion is granulated with excipients to form pellets or sprayed onto pellets in order to achieve controlled drug release. The drug homogeneously distributed within the polymer is dissolved, dispersed or dissolved and dispersed. These systems present several advantages as easy manufacture and low cost (1 step process), lower risk of dose dumping (if the coating accidentally ruptures) and the possibility of improvement of aqueous drug solubility. Besides drug-polymer interactions can occur and bring benefits in terms of mechanical properties such plasticizing effect. The main disadvantages include fast initial release and incomplete release in a defined time. The latter could be avoided by coating sugar cores with different polymer: drug ratios, in which the drug was more concentrated in deeper layers of the matrix and so counteracting for the increased diffusion pathway. In addition matrix system, were found suitable to control drug release of a highly soluble drug.

Classification of Matrix tablet[10-15,17]

On the basis of retardant material used matrix tablet can be divided into 5 types

A) Hydrophobic matrices

B) Hydrophilic matrices

C) Fat-wax matrices

D) Biodegradable matrices

E) Mineral matrices

On the Basis of porosity of matrix[13, 16]

A) Macro porous system

B) Micro porous system

C) Non –porous system

Polymers used in matrix tablet[13, 16]

- Hydrogels
- Soluble polymers

- Biodegradable polymers
- Non-biodegradable polymers
- Mucoadhesive polymers

Advantages of matrix system

- Easy to manufacture.
- Versatile, effective and low cost.
- Can be made to release high molecular weight compounds.
- Their capacity to incorporate active principle is large, which suits them to delivery of large dosage.[18]

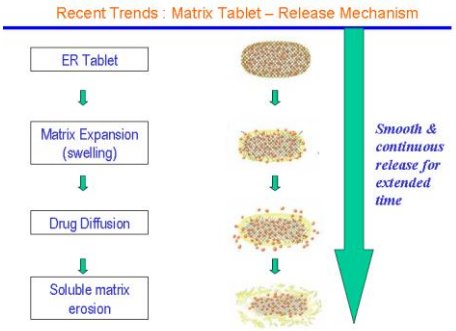

Figure 1.1: Mechanism of drug release from Matrix system.

2. MATERIALS AND METHODS

2.1 Material used

The following drugs, excipients/polymers and chemicals were used for the Formulation and evaluation of Extended release matrix tablet.

2.1 List of chemicals

Table 2.1: List of Drug, Excipients / Polymer and Solvent.

Sr. No	Drug/ Excipient/ Polymer	Manufacturer
1	Carvedilol phosphate	Qualitekpharma, jeedimetla, Hyderabad
2	Hydroxy propyl methyl cellulose K4M	Drug India, Hyderabad
3	Sodium CMC	Drug India, Hyderabad
4	Magnesium stearate	Drug India, Hyderabad
5	Microcrystalline sodium PH 102	Drug India, Hyderabad
6	Lactose	Drug India, Hyderabad
7	Talc	Drug India, Hyderabad

2.2 List of equipments

Following equipments were used for the preparation and evaluation of tablet.

Table 2.2: List of equipments.

Sr. No	Instruments	Manufacturer
1	Single pan electronic balance	Schimadzu AUX220, Japan.
2	Infrared spectrophotometer	Schimadzu 8400S
3	UV spectrophotometer	Schimadzu UV1800
4	Differential scanning calorimeter	Schimadzu DSC- 60
5	Stability chamber	Bombay Lab services
6	Hardness tester (Monsanto type)	Rolex Scientific Engineers Limited
7	Friability apparatus	Electrolab EF2. Mumbai.
8	Dissolution apparatus	Electrolab ETC11L. Mumbai.
9	Rotary tablet punching press	Karnavati (rimek)
10	Bulk density apparatus	Electrolab ETD1020. Mumbai.
11	Vernier calliper	Mitutoyo

2.3 Preformulation study of drug[19, 20]

2.3.1 Identification of drug

- **Colour, odour and appearance**

The drug sample was evaluated for its colour, odour and appearance.

- **Melting point determination**

Melting point of the drug sample was determined by capillary method by using Melting point apparatus and can also be recorded from DSC graph.

- **Fourier Transformation Infra-red (FTIR) analysis**

Infra-red spectroscopy analysis was performed by Fourier Transform Infrared Spectrophotometer.

- **Differential scanning calorimetry (DSC)**

DSC was performed in order to assess the thermotropic properties and thermal behavior of Carvedilol phosphate. About 5 mg of the sample were sealed in the aluminum pans and heated at the rate of 10^0C/min, covering a temperature range of 40^0C to 300^0C under nitrogen atmosphere of flow rate 100 ml/min.

- **Ultraviolet (UV) spectroscopy**

UV spectrum of 100 µg/ml solution of the drug powder in 0.1 N aqueous hydrochloric acid solution, water and Phosphate buffer pH 6.8 was recorded in the range of wavelengths from

200 nm to 400 nm using UV-visible Double beam Spectrophotometer (UV-Chemito-2600).

➢ **Determination of solubility[19]**

A solvent under consideration (water, 0.1N HCl and phosphate buffer solution pH 6.8) was saturated with the drug powder and the vials were allowed to stand at room temperature (25°C) for 7 days with frequent shaking. The solution was filtered using Whatmann filter paper. The filtrate was analyzed for drug content using Ultraviolet (UV) spectroscopy.

2.3.2 Compatibility study of drug with polymers

Carvedilol phosphate was mixed with polymers and excipients in different ratios and were placed in amber colored vials. Vials were sealed and kept in the stability chambers at various conditions of temperature and humidity for one month.

Table 2.3: Relationship between temperature and relative humidity

Temperature	Humidity condition
25^0C	65% RH
40^0C	75% RH
50^0C	65% RH

Samples were analyzed by FTIR Spectrophotometer for any deviation in IR spectra by comparing with standard spectra.

2.3.4 Determination of powder Charactertics[20]

➢ **Density**

The bulk density was determined by gently pouring the powders into a 100 ml volumetric cylinder up to a total volume of 90 ml. After weighing the above volume of powder, the bulk density was determined using equation as presented below.

Density = Weight (gm)/Volume (ml)…

For the measurement of tap density, the cylinder was tapped over a 0.5 inch vertical drop, using a tap density tester, until a constant volume was observed.

➢ **Compressibility and Hausner Ratio.**

From the above results, the compressibility of the powder was calculated as the following ratios.

Compressibility (%) = {1 – bulk density/tap density} × 100…

The Hausner ratio is defined as the ratio between tap and bulk density of powders.

Angle of Repose[21]

The angle of repose (θ) for each powder was determined by placing the powder in a funnel with the following critical dimensions: orifice diameter 10 mm and base diameter 65 mm. The tip of the orifice of the funnel was at fixed height from the ground horizontal surface, and the powder was allowed to flow only under the force of gravity. The angle of repose, θ was calculated from the following relationship.

$$\tan \theta = h/r, \qquad \text{Hence, } \theta = \tan^{-1} h/r$$

(Where *h* is height of the pile of powder and *r* is the radius of the base of cone).

2.4. Formulation and Development

2.4.1 Dose Selection

The 80 mg daily dose of Carvedilol phosphate has been shown to be safe and effective in clinical studies as in marketed capsule formulation. Therefore 80 mg of Carvedilol Phosphate was selected for the designing of extended drug delivery system in the present study.

2.4.2 Formulation of Blended Tablet

Formulations were prepared by using **n**ine different combinations of two polymers. Mixing of drug, polymers and other ingredients was done by geometric mixing. Tablets were prepared by direct compression method using rotary press. Compression force for all the Tablets was adjusted to get Tablets of hardness 3.5- 6 kg/cm2. Weight of Tablets was adjusted to 500 mg as shown in Table2.4.

Table 2.4: Formula for Blended Formulation.

Ingredient(mg)	FORMULATION								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carvedilol phosphate	80	80	80	80	80	80	80	80	80
HPMC K4M	200	180	190	140	120	100	80	60	40
Sodium CMC	20	40	60	80	100	120	140	460	180
Mg, stearate	4	4	4	4	4	4	4	4	4
Talc	1	1	1	1	1	1	1	1	1
MCC PH102	120	120	120	120	120	120	120	120	120
Lactose	75	75	75	75	75	75	75	75	75
Total Weight	500	500	500	500	500	500	500	500	500

2.4.3 Preparation of powder blend

Powder blend were prepared for the preparation of extended tablet by direct compression method. All the ingredients were weighed accurately and mixed by passing through 60 # sieve. Mixing was again done by spatulation and tumbling in glass mortar and pestle.

2..4.4 Evaluation of powder blend

- **Angle of Repose**[21]

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of angle of granules on the paper. The angle of repose was calculated by substituting the values of the base radius and pile height in the following equation,

$$\tan \theta = h/r, \qquad \text{Hence, } \theta = \tan\text{-}1\ h/r$$

Where,

θ = Angle of repose, h = Height of the cone, r = Radius of the cone base.

Table 2.5: Relationship between Angle of Repose (θ) and Flowability.

Angle of Repose (θ)	Flow ability
< 20	Excellent
20 – 30	Good
30 – 34	Passable
> 40	Very Poor

- **Carr's Compressibility Index**[20]

An indirect method of measuring powder flow from bulk densities was developed by Carr's. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below:

$$\% \text{ Compressibility} = \frac{Df - Do}{D_f} \times 100 \ldots.$$

Where,

D_F = Fluff or Poured bulk or bulk density.

D_o = Tapped or Consolidated bulk density.

Carr's Compressibility Index (%) = [(TBD-LBD) X 100] / TBD.

Table 2.6: Relationships between % compressibility and flowability.

% Compressibility	Flowability
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
> 40	Extremely Poor

➢ **Bulk Density and Tapped Density**[20]

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 20 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 100 ml 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 2.5 cm at 2-second intervals. The tapping was continued until No further change in volume was noted. LBD and TBD were calculated using the following formulas.

➢ **Hausners ratio**[20]

Hausners ratio = TBD/LBD

LBD = Weight of the powder/ Volume of the packing

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

Table 2.7: Type of flow and Hausner ratio.

Hausners ratio	Type of flow
Less than 1.25	Good Flow
1.25 – 1.5	Moderate
More than 1.5	Poor Flow

2.5 Preparation of Tablet

Powder blend were prepared for the preparation of extended tablet by direct compression method. All the ingredients were weighed accurately and mixed by passing through 60 # sieve. Mixing was again done by spatulation and tumbling in glass morter and pestle.

2.5.1 Evaluation of extended release tablets.

All the prepared floating tablets were evaluated for following official and unofficial parameters.

➢ **Appearance**[22]

The tablets were identified visually by checking the difference in color.

➢ **Thickness**[23]

The thickness of the tablets was determined using a Vernier Caliper. Twenty tablets from each batch were used and mean ± SD was calculated.

➢ **Hardness**[23]

Hardness was measured using Monsanto tester. For each batch five Tablets were tested.

- **Friability**[22]

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were dedusted and weighed again. The percentage friability was measured using formula,

$$\% F = \{1-(Wt/W)\} \times 100$$

Where,

% F = Friability in percentage

W = Initial weight of tablets

Wt = Weight of tablets after revolution

- **Weight variation**[22]

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation if not more than two of the individual tablet weight deviate from the average weight.

Table 2.8: Weight variation test.

Sr. No	Average wt. of tablet		% of Deviation
	I.P.	U.S.P.	
1	80 mg or less	130 or less	± 10
2	> 80 to < 250 mg	> 130 to < 324 mg	±7.5
3	more than 250	more than 324	±5

- **Drug content uniformity**[24]

Twenty randomly chosen tablets from each formulation were thinly powdered in a mortar and a portion of the resulting powder equal to the weight of the respective tablet was solubilized in phosphate buffer ph 6.8 in 100ml volumetric flask and further diluted with phosphate buffer to make a solution of Carvedilol Phosphate as per the standard concentration of calibration curve and assayed spectrophotometrically at 238 nm. Each measurement was carried out in triplicate and the results are averaged. A blank solution containing all the components, except for the drug, was also prepared. Corresponding concentrations were calculated from the standard curve.

- ***In vitro* dissolution studies**[25]

The release rate of Carvedilol phosphate from extended release tablets was determined. The dissolution test was performed using United States Pharmacopoeia (USP) type II (paddle)

apparatus, 900ml of 6.8 phosphate buffer at 37 ± 0.5°C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at the appropriate time for 24 hours, and the samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 238 nm using a Spectrophotometer Schimadzu UV1800. Cumulative percentage drug release was calculated using PCP Disso Version V3 software. The drug content was calculated using the equation generated from standard calibration curve. The % cumulative drug release was calculated.

2.5.2 Kinetics studies[17]

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. Based on the r-value, the best-fit model was selected.

- **Zero order kinetics**

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and No equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_o + K_o t \ldots$$

Where, Q_t = amount of drug dissolved in time t.

Q_o = initial amount of the drug in the solution and

K_o = zero order release constant.

- **First order kinetics**

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$\text{Log } Q_t = \log Q_o + K_1 t/2.303.$$

Where,

Q_t = the amount of drug released in time t,

Q_o = the initial amount of drug in the solution and

K_1 = the first order release constant.

- **Higuchi model**

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions

were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$$Q_t = K_H \cdot t^{1/2}$$

Where, Q_t = amount of drug released in time t,

K_H = Higuchi dissolution constant.

- **Korsmeyer and Peppas release model**

To study this model the release rate data are fitted to the following equation,

$$Mt / M = K \cdot t^{n}$$

Where Mt / M is the fraction of drug release, K is the release constant, t is the release time and n is the diffusional coefficient for the drug release that is dependent on the shape of the matrix dosage form.

2.5.3 Stability studies[26]

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions.

Long-Term Testing: 250 C ± 20 C / 60% RH ± 5% for 12 Months

Accelerated Testing: 400 C ± 20 C / 75% RH ± 5% for 6 Months

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 400 C / 75% RH for 3 months and evaluated for their physical appearance, drug content and drug excipients compatibility at specified intervals of time.

3. RESULT

3.1. Preformulation study of drug

Formulation development requires in depth understanding of physical, chemical, engineering and biological principles and application of these principles. The design of controlled release dosage forms should take into account three important criteria viz. drug, delivery and destination of the delivery system. Pre formulation studies help in studying the physicochemical properties of drug.

3.1.1 Identification of drug

The received drug sample was identified by using various tests. The results are presented in Table 3.1.

Table. 3.1: Identification Tests of Drug Sample.

Identification test	Results of sample obtained	Reported standards
Appearance	Fine powder	Fine powder
Colour	Off white	Off white
Odor	odorless	Odorless
Melting point	114.2^0c	$114\text{-}117^0$c

3.1.2 Solubility determination.

Table 3,2: Solubility data of Carvedilol phosphate.

Sr.No.	Medium	mg/ml
1	0.1 N HCl	0.22
2	Phosphate Buffer pH 6.8	0.34

3.1.3. UV Spectroscopy of Carvedilol phosphate

- **Determination of λ max**

Standard concentration of 100 µg/ml of Carvedilol phosphate was prepared and scanned in the range of 200.0 to 400.0 nm by using UV detector. The spectrum was recorded and at the 238. nm wavelength it shows more responsive.

- **Preparation for calibration curve of Carvedilol phosphate**

It was determined as per procedure given in experimental work. The graph of correlation between concentration and absorbance values of Carvedilol phosphate in Phosphate buffer PH6.8 shows the linearity of the standard preparation. The correlation coefficient value (R^2) in Phosphate buffer ph6.8 was found to be 0.999**,** Y= 0.019x-0.009.

➢ **Differential scanning calorimetry**

The DSC thermogram of the drug depicts a sharp endothermic peak at 114.6°C corresponding to the melting transition temperature and decomposition of Carvedilol Phosphate.

➢ **Drug-Excipient compatibility study by FTIR**

The FT-IR analysis of the Carvedilol Phosphate. was carried out for qualitative compound identification. The FT-IR spectrum for pure drug was carried out by KBr disc method for pure drug Carvedilol Phosphate, physical mixture of Carvedilol phosphate + HPMC K4M and Carvedilol phosphate+ sodium CMC. the spectrum was recorded in the range of 4000 cm-1 and 450cm-1.

3.2 Determination of powder characteristics

Powder characteristics of drug affect formulation of tablets. Results shown in Table 3.3 indicated that the drug powder was fairly good flowing. Values of angle of repose revealed that the drug powder was passable.

Table 3.3: Powder characteristics of Carvedilol phosphate.

Sr. No	Parameters	Specifications
1	Loss on Drying (%)	0.4
2	Bulk density (g/cc)	0.321
3	Tapped Density (g/cc)	0.406
4	Compressibility index (%)	21.68
5	Hausner's ratio	1.26
6	Angle of repose (□ ')	27°4'
7	Melting point (□C)	114.2
8	Residue on ignition (%)	0.1

3.3 Formulation and Development

3.3.1 Evaluation of Pre compressible Blend

Table 3.4: Determination of Flow Property of final granules of Formulation Batches F1- F9.

Formulation Code	Bulk density (gm /ml) ±SD* mmmmmlmcc)	Tapped density (gm/ml) ± SD*	Hausner ratio ± SD*	Carr's index (%) ± SD*	Angle of repose (θ) ± SD*
F1	0.317± 0.007	0.376 ± 0.0015	1.18± 0.015	15.69 ± 1.44	26.38 ± 1.01
F2	0.291± 0.001	0.331 ±0.009	1.19 ± 0.018	12.11± 1.21	27.14 ± 1.05
F3	0.307± 0.0015	0.347± 0.0016	1.13 ± 0.011	12.26 ± 1.24	26.85 ±1.03
F4	0.326±0.001	0.384 ± 0.0010	1.17 ±0.016	15.10 ±1.40	29.12± 1.11
F5	0.286±0.001	0.342 ± 0.0011	1.19 ± 0.018	16.37 ± 1.47	28.47 ± 1.09

F6	0.301±0.004	0.350 ± 0.0010	1.16 ± 0.013	14.00 ±1.37	26.96 ± 1.03
F7	0.298±0.001	0.344 ±0.0011	1.15 ± 0.012	13.33± 1.32	25.72 ± 1.12
F8	0.286±0.001	0.351± 0.0012	1.22 ± 0.021	18.51± 1.82	26.41 ± 1.04
F9	0.299±0.002	0.344 ± 0..0011	1.15 ± 0.013	13.08 ± 1.31	24.51 ± 1.10

* All values are mean ± SD, (n = 3).

3.3.2Compression of blends

Different blends of Batches F1-F9 were compressed as per procedure. Tablets were prepared by direct compression method using rotary press. Compression force for all the Tablets was adjusted to get Tablets of hardness 3.5- 6 kg/cm2. Weight of Tablets was adjusted to 500 mg.

3.3.3 Evaluation of the Carvedilol phosphate tablet

Table 3.5: Determination of evaluation Parameter of Batch F1-F9.

Formulation code	Weight variation ±SD* (n=20)	Hardness (Kg/cm^2) ± SD*	Friability (%) ± SD* (n=20)	Thickness (mm) ± SD*	Content uniformity ± SD*(%)
F1	498± 2.08	6.4 ± 0.0015	0.72± 0.025	3.8 ± 0.20	99.28 ± 2.05
F2	499± 2.10	6.3 ±0.009	0.68 ± 0.018	3.6± 0.16	97.16± 2.08
F3	497±2.05	6.7± 0.0016	0.69 ± 0.021	3.7 ± 0.18	101.1 ±2.12
F4	501±2.12	6.6 ± 0.0010	0.66 ±0.022	3.8 ±0.20	97.68± 2.01
F5	498±12.08	6.7 ± 0.0011	0.68 ± 0.018	3.8 ± 0.20	99.41± 2.06
F6	497±2.09	6.9 ± 0.0010	0.65 ± 0.021	3.6 ±0.16	98.19 ± 2.04
F7	496±2.05	7.2 ±0.0011	0.67 ± 0.020	3.8± 0.20	99.6 ± 2.10
F8	502±2.15	7.1± 0.0012	0.65 ± 0.021	3.8± 0.21	99.5 ± 2.03
F9	501±2.12	6.8 ± 0..0011	0.70 ± 0.020	3.8 ± 0.20	99.6 ± 2.05

* All values are mean ± SD, (n = 3).

3.3.4 Dissolution profile of Carvedilol phosphate tablet

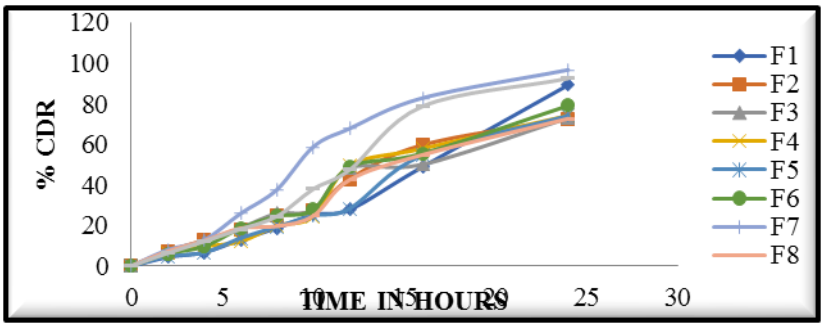

Figure 3.1: Cumulative % drug released of F1-F9 formulations.

In dissolution profile of Carvedilol Phosphate batch F7 gives the 98.11% drug released. F7 release was good as compared to other batches.

3.3.5. Drug release kinetics model

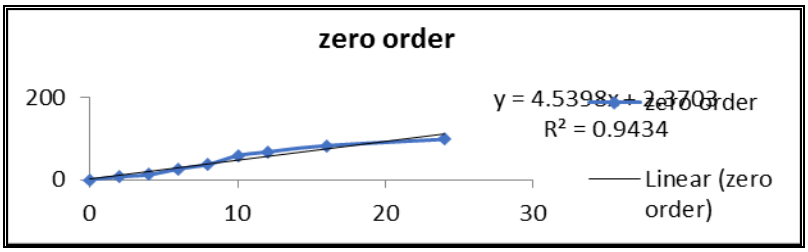

Figure 3.2: zero order kinetics of F7.

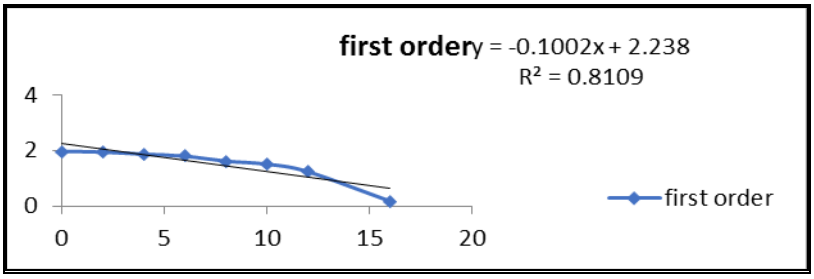

Figure 3.3: first order kinetics of F7.

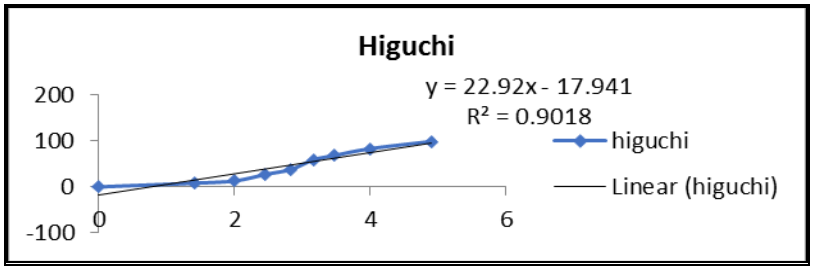

Figure 3.4: Higuchi model of F7.

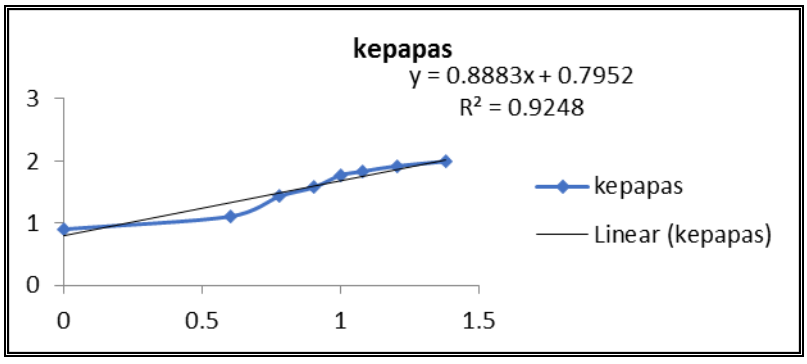

Figure 3.5: Korseymey-peppas model of F7.

3.3.6. Stability Study[26]

The stability studies were conducted of batch no.7 and the dissolution profile of batch no.7 was found more precise than the other batches so that only batch no.7 was mentioned here for stability studies.

The stability studies were conducted in intermediate and accelerated conditions. The selected tests, results & their comparison were mentioned here in following tabular, graphical form.

Table No.3.6: Evaluation of parameter Stability at 30°C/75%RH for batch F7.

Parameter	1 Month	2 Month	3 Month
appearance	White	White	White
Thickness	3.8 ± 0.20	3.8±0.20	3.8±0.20
Hardness	7.2 ± 0.07	6.8±0.03	7.1±0.08
Drug content (%)	99.6 ± 2.10	99.3±2.13	98.6±2.5

* All values are mean ± SD, (n = 3).

Table No.3.7: Evaluation of parameter Stability at 40°C/75%RH for batch F7.

Parameter	1 Month	2 Month	3 Month
appearance	White	White	White
Thickness	3.8±0.20	3.8±0.20	3.8±0.20
Hardness	7.2±0.07	7.0±0.08	7.1±0.08
Drug content (%)	99.6±2.10	99.3±2.13	98.4±2.5

* All values are mean ± SD, (n = 3).

4. DISCUSSION

4.1 Preformulation study of drug

4.1.1 Identification

The received drug sample was identified by using various tests. The results shows that those are in accordance with reported valies.

4.1.2 Solubility

According to above results, phosphate buffer $_{P}$H 6.8 shows more solubility than other media so that Phosphate buffer $_{P}$H 6.8 used for further study.

4.1.2 UV Spectroscopy of Carvedilol phosphate

- **Determination of λ max**

The spectrum was recorded and at the 238. nm wavelength it shows more responsive.

- **reparation for calibration curve of Carvedilol phosphate**

The value of r^2 is 0.999. On the basis of obtained results; it was concluded that Carvedilol phosphate obeys Beer- Lambert"s law in the range of 1-12 µg/ml.

- **Differential scanning calorimetry**

The thermogram showed individually for drug Carvedilol phosphate nearly unchanged as

compared to thermogram of physical mixture. Hence, it can be concluded that there was no interaction between drug and physical mixture.

- **Drug-Excipient compatibility study by FTIR**

In drug –polymer compatibility studies there was no physicochemical interaction between drug and polymers.

4.2 Determination of powder characteristics

Results obtained indicated that the drug powder was fairly good flowing. Values of angle of repose revealed that the drug powder was passable.

4.3 Formulation and Development

4.3.1 Evaluation of Pre compressible Blend

From the Table3.4, it was confirmed that in process powder blend exhibited good flow property. All formulations were evaluated for bulk density which ranged from 0.26-0.33 (g/mL), tapped density ranged from 0.31-0.39 (g/mL), Carr's index ranged from 12.23% - 18.23%, angle of repose ranged from 24º to 26° and the Hausner's ratio was found in the range of 1.14-1.19. All these results indicated that, the powder blend showed good flow properties.

4.3.2 Compression of blends

Powder blend were prepared for the preparation of extended tablet by direct compression method. All the ingredients were weighed accurately and mixed by passing through 60 # sieve. Mixing was again done by spatulation and tumbling in glass morter and pestle.

4.3.3 Evaluation of the Carvedilol phosphate tablet

From the above table, the results showed that all trial tablets have their weight within 497 to 502 mg tablet. The formulation batch1 and batch 9, all batch have the sufficient hardness i.e., with in the limit. All the tablets of different trials were uniform in diameter (3.8 mm). According to Friability parameter, the tablets of trials F1 and F9 trials were within the prescribed limits.

4.3.4 Dissolution profile of Carvedilol phosphate tablet

In dissolution profile of Carvedilol Phosphate batch F7 gives the 98.11% drug released. F7 release was good as compared to other batches

4.3.5. Drug release kinetics model

The kinetic investigation of the release profile gave us useful insight into the mechanism of drug release from the tablets. The release did not show any burst effect or lag time, which is indicative of a homogeneous drug distribution in the polymer matrix. The dissolution data was subjected to regression analysis and were fitted to kinetic models, viz., Zero order, First order, Peppas and Higuchi. It was found that most of the formulations followed Zero order and K- peppas release.It describes the systems where the drug release rate is independent of its concentration of the dissolved substance.

4.3.6. Stability Study

In case of stability studies the assay results was found within limits.1 month, 2 months, 3 months Dissolution profile was comparatively matches the initial dissolution profile with little fluctuation.

5. CONCLUSION

In pre formulation studies Carvedilol Phosphate was found to be off- white in colour, odorless, tasteless. In UV estimation calibration curve of Carvedilol Phosphate in phosphate buffer ph 6.8 given r^2 value is 0.999 and λ max = 238nm on the basis of obtained results; it was concluded that Carvedilol Phosphate obeys Beer- Lambert's law in the range of 1-12 µg/m.

In DSC thermogram of the drug depicts a sharp endothermic peak at 114.9°C corresponding to the melting transition temperature and decomposition of Carvedilol Phosphate. Such sharp endothermic peak signifies that Carvedilol Phosphate used was in pure state and same was also observed in physical mixture. The thermogram showed individually for drug Carvedilol Phosphate nearly unchanged as compared to thermogram of physical mixture. Hence, it can be concluded that there was no interaction between drug and physical mixture.

In FTIR studies spectrum of Carvedilol Phosphate shown all peaks corresponding to functional group presents in the structure of Carvedilol Phosphate and there was no physicochemical interaction between drug and polymers.

All blended formulations were evaluated for bulk density which ranged from 0.26-0.33 (g/mL), tapped density ranged from 0.31-0.39 (g/mL), Carr's index ranged from 12.23% - 18.23%, angle of repose ranged from 24º to 26° and the Hausner's ratio was found in the

range of 1.14-1.19. All these results indicated that, the powder blend showed good flow properties. All tablet formulation has their weight within 498 to 501 mg tablet. The formulation batch F1 and batch F9, all trials have the sufficient hardness i.e., with in the limit. All the tablets of different trials were uniform in diameter (3.8 mm). According to Friability parameter, the tablets of batch F1 and batch F9 trials were within the prescribed limits.

In dissolution studies formulation F7 given best drug release up to the 24 hrs compared to other formulation and it follows zero order kinetics. In case of intermediate and accelerated stability studies the results were found within limits.1 month, 2 months, 3 months Dissolution profile was comparatively matches the initial dissolution profile with little fluctuation.

Regulated drug release in zero-order manner attained in the current study indicates that the optimized extended release tablet of Carvedilol Phosphate, prepared using Sodium carboxymethyl cellulose and HPMC K4M can successfully be employed in oral controlled release drug delivery system. Modified release ability of the formulation is likely to increase its GI residence time, and eventually, improve the extent of bioavailability. However, appropriate balancing between various levels of the two polymers is imperative to acquire proper controlled release. Extended release tablet of Carvedilol Phosphate can be successfully employed to treat hypertension and congestive heart failure condition. Extended release tablet of Carvedilol Phosphate will reduce the frequency of administration of drug and helps to minimize dose of drug and side effects associated with the drug.

Since the polymer and the drugs were found to be compatible and the release mechanism is characterized, there is a great scope for the formulation of extended-release tablet of Carvedilol Phosphate will reduce the frequency of administration of drug and helps to minimize dose of drug and side effects associated with the drug.

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