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Formulation and evaluation of sustain release matrix tablets of carvidolol phosphate

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ABSTRACT

The purpose of the present study was to formulate and evaluate once daily sustained release matrix tablets of carvidolol phosphate. . Carvedilol Phosphate is a nonselective beta blocker indicated in the treatment of mild to severe congestive heart failure Various formulations of sustained release tablets of Carvidolol phosphate were developed using various polymers Guargum, SCMC, HPMC100M in different concentrations by direct compression method. Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias and a standards reference. Results of in-vitro release profile indicated that formulation(F9) was the most promising formulation as the extent of drug release from this formulation was high(100.75 %) as compared to other formulations.From the above results and discussion it is concluded that formulation of sustain release tablets of carvidolol phosphate containing Guar gum (33.33%) ,formulation F9 can be taken as an ideal for optimized formulation of sustain release tablets for 24 hours release as it fulfills all the requirements for sustained release tablets.

Introduction

Carvedilol is used to treat heart failure (condition in which the heart cannot pump enough blood to all parts of the body) and high blood pressure. It also is used to treat people whose hearts cannot pump blood well as a result of a heart attack. Carvedilol is often used in combination with other medications. Carvedilol is in a class of medications called beta-blockers. It works by relaxing blood vessels and slowing heart rate to improve blood flow and decrease blood pressure. Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in determined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy andconstant delivery. There are certain considerations for the preparation of extended release formulations: If the active compound has a long half-life, it is sustained on its own, If the pharmacological activity of the active 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. The polymers used in the present work are hydrophilic polymers ,guar gum ,HPMCK 100M and sodium carboxyl methyl cellulose. All these three polymers used were highly viscosity polymers. The direct compression technique, which is dry process, is also known to be a more economical process than other techniques. In the present investigation the objective is to prepare directly compressed matrix tablets for sustained release of Carvidolol phosphate and evaluate the tablets for in vitro drug release studies.

Materials and methods

Carvedilol phosphate procured by Symed labs ltd, Hydrabad, Guar gum and Sodium Carboxy methyl cellulose ,Lactose purchased by Qualines ,New Delhi, HPMC K100 M CR gift sample by Cadila Pharm, Ahmedabad

Table-1 Composition F1-F5 matrix tablets formulations containg SCMC

Ingredients(Mg)		F1	F2	F3	F4	F5
Drug		20	20	20	20	20
SCMC		40	60	80	100	120
Lactose		234	214	194	174	154
Magnesium stearate		2	2	2	2	2
Talc		4	4	4	4	4
Total		300	300	300	300	300

Formulation matrix tablets of carvedilol phosphate[2,3,4]

Preparation of carvedilol phosphate matrix tablets

All the matrix tablets, each containing 20 mg of carvedilol phosphate were prepared by direct compression method. Accurately weighted amounts of drug, polymer, and diluents were mixed geometrically in a morter. This mixture was passed through no.80 sieve and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then blend was then lubricated with magnesium stearate and talc for 2 minutes and compressed into tablets on a rotator machines using 9 mm round, flat-faced punches. In the formulations prepared , the retardants included were hydrophilic polymers.HPMCK100M, Guar gum, sodium carboxy methyl cellulose. Lactose was used as diluents, magnesium stearate and talc were used as lubricant.

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Composion of different formulation were given in the following tables

Table-2 Composition F1-F5 matrix tablets formulations containing Guar gum

Ingredients(Mg)	F6	F7	F8	F9
Drug	20	20	20	20
Guar gum	40	60	80	100
Lactose	234	214	194	174
Magnesium stearate	2	2	2	2
Talc	4	4	4	4
Total	300	300	300	300

Table-3. Composition F1-F5 matrix tablets formulations containing HPMCK100M

Ingredients(Mg)	F10	F11	F12
Drug	20	20	20
HPMC K 100M	60	80	100
Lactose	214	194	174
Magnesium stearate	2	2	2
Talc	4	4	4
Total	300	300	300

Characterization of polymer and granules of formulations[7,11,14,15,22,23]

Bulk density

The bulk density was determined by gently pouring the powders into a 100 mL volumetric cylinder 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)

Tapped Density

It was determined by placing a graduated cylinder, containing a known mass of drug or polymer coated granules, on mechanical tapping apparatus, which was operated for a fixed number of taps until the powder bed volume has reached a minimum. Using the weight of a powder or coated granules in a cylinder and this volume, the tapped density was computed.

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.

Evaluation of physical properties of matrix tablets:

The prepared matrix tablets Carvedilol phosphate were evaluated for the following Parameters were shown in table.

Weight variation:

Twenty (20) tablets from each batch were individually weighed in milligram (mg) on digital balance. The average weight and standard deviation were calculated and the results were expresses as compliance or non-compliance of set limits.

Tablet thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Digimatic digital outside micrometer (Mitutoyo, Japan). The average thickness and standard deviation were reported.

Tablet hardness:

Tablets hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness, and standard deviation was reported.

Friability:

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

Determination of drug content of matrix tablets:[15,18,19,27]

The drug content of the matrix tablets was determined according to in house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the stated amount.

Procedure: Ten tablets with pre determined weight from each batch were taken and crushed in a mortar and weight equivalent to one average tablet was taken, transferred to a 250 ml volumetric flask 50 ml of methanol was used to solubilize the Ciprofloxacin and 0.1N HCl was added. The flask was shaken over the cyclomixer. It was taken out and the solution was filtered using membrane filter. Then filtrate was sufficiently diluted with 0.1 N HCl and by spiking the sample the peak area was recorded at 276 nm. The drug content of the standard and the control containing drug powder and with out Drug respectively were determined. The drug content was determined by the formula. The absorbance of control was deducted from test and standard. Drug content was determined by using UV-visible spectroscopy.Result are shown in table

$$\% \text{ Drug content of the batch} = \frac{\text{Amount in test}}{\text{Amount in standard}} \times 100$$

Results

Comparative percentage drug release of marketed formulation and optimized formulation F9

The % drug release profile of marketed formulation and F9 formulation in shown in graph. Marketed formulation (Cardivas) showed 95% of drug release upto 12 hrs only. The prepared F9 formulation showed sustained release (100.75%) upto 24 hrs. comparing the both formulations the prepared matrix tablets showed good sustained action than the marketed formulation.

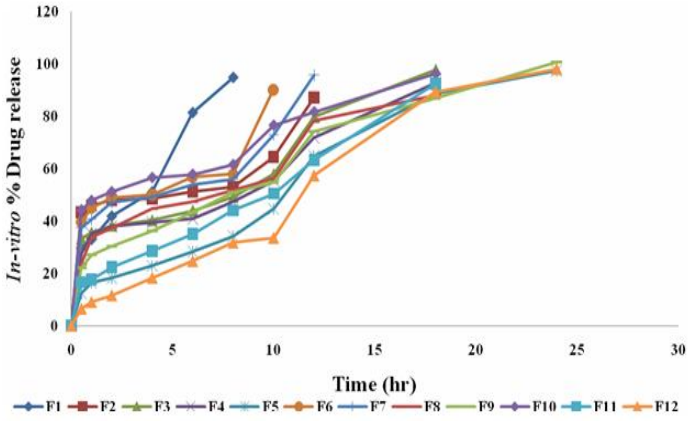

Figure-1 *In-vitro* drug release of Carvedilol phosphate

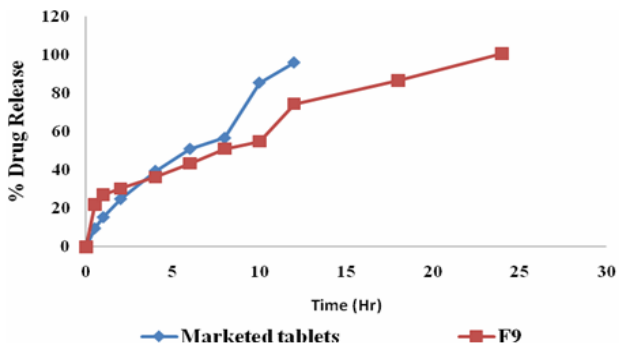

Figure-2 Comparative percentage drug release of marketed formulation and optimized formulation F9

Table: 1 Physical property of compressed matrix tablets

Formulation code	Angle of repose mean SE, N=3	Bulk Density mean SE, N=3	Tapped Density	Carrs Index(%)
F1	20.33± 0.042	0.614± 0.005	0.751	10.74
F2	23.96± 0.01	0.608± 0.003	0.764	13.38
F3	18.21±0.02	0.576 ± 0.004	0.722	12.28
F4	18.10±0.03	0.641± 0.001	0.688	10.11
F5	19.51±0.057	0.624 ± 0.12	0.776	12.82
F6	21.11+0.026	0.620± 0.11	0.697	13.39
F7	20.64±0.023	0.621 ± 0.11	0.729	12.17
F8	24.14±0.042	0.618 ± 0.05	0.727	11.38
F9	18.19±0.06	0.622 ± 0.07	0.706	12.60
F10	21.18±0.02	0.581 ± 0.031	0.672	11.90
F11	24.18+0.41	0.575 ± 0.012	0.766	10.07
F12	24.13±0.051	0.624 ± 0.07	0.699	12.52

Table 2: Physical properties of compressed matrix tablets

Formulation code	Hardness (kg/cm2)	Thickness (mm)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	6.10 ±0.25	3.2 ±0.12	2.30	0.39± 0.07	97.89± 3.29
F2	5.87 ±0.40	3.2 ±0.11	1.90	0.43± 0.06	100.62± 2.98
F3	5.08 ±0.27	3.1 ±0.03	1.32	0.42± 0.04	102.13± 3.12
F4	6.15 ±0.41	2.9 ±0.06	2.08	0.38± 0.05	97.99± 3.19
F5	5.78 ±0.12	3.2 ±0.078	2.01	0.49± 0.03	99.15± 4.11
F6	5.65 ±0.32	3.2 ±0.067	1.04	0.45± 0.05	95.87± 2.67
F7	6.12 ±0.3	3.1 ±0.06	1.02	0.37± 0.03	100.11± 2.98
F8	5.09 ±0.11	3.2 ±0.06	2.01	0.38± 0.01	99.14± 2.78
F9	6.16 ±0.40	3.2 ±0.03	2.05	0.46± 0.02	98.14± 3.18
F10	5.57 ±0.10	2.9 ±0.05	1.98	0.41± 0.05	96.45± 3.66
F11	6.09 ±0.21	3.1 ±0.1	1.56	0.46± 0.03	103.16± 2.89
F12	5.35 ±0.11	3.1 ±0.03	1.82	0.43± 0.04	95.98± 2.99

Table-3 *In-vitro* drug release of Carvedilol phosphate

Time (Hr)	*In-vitro* drug release of Carvedilol phosphate											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.5	29.96 0.05	43.34 0.06	33.33 0.23	27.53 0.34	12.49 0.12	39.73 0.39	37.53 1.73	23.50 0.59	22.08 0.71	44.28 2.13	16.75 0.02	6.51 0.12
1	33.02 0.07	45.95 0.001	35.59 0.03	35.26 0.25	16.47 1.12	45.04 2.12	40.76 1.71	33.93 2.02	27.06 2.07	47.85 1.09	17.73 0.01	9.09 0.04
2	41.91 0.09	48.1 0.12	38.21 0.09	38.06 0.12	18.33 0.06	49.08 1.16	47.21 2.30	37.50 0.05	30.35 0.34	51.19 0.09	22.45 0.03	11.63 0.01
4	51.2 0.12	48.6 1.02	40.26 0.06	39.57 0.15	22.87 0.13	50.06 1.14	49.12 2.97	44.81 5.27	36.32 1.86	56.62 0.02	28.67 0.09	18.32 0.23
6	81.44 0.45	51.23 0.02	44.03 0.05	41.03 0.12	28.27 1.07	56.96 0.16	53.89 1.51	47.36 0.43	43.44 1.72	57.82 1.04	35.05 0.01	24.7 0.23
8	94.87 0.03	53.05 0.15	49.19 2.13	47.47 0.14	34.17 0.17	57.98 0.06	56.02	51.95 2.77	51.08 1.68	6.54 0.03	44.12 1.04	31.70 0.34
10		64.46 0.34	57.92 1.04	55.31 0.09	44.66 0.04	90.26 1.09	73.04 1.40	56.08 1.62	54.91 2.16	76.60 0.04	50.52 2.05	33.60 0.27
12		87.23 0.05	79.70 0.05	71.81 0.34	64.79 1.08		95.79 2.08	78.34 1.12	74.34 0.51	81.69 0.06	63.32 0.03	57.40 0.14
18			97.81 0.07	92.85 0.13	88.78 0.13			88.02 1.96	86.89 2.80	96.27 0.01	92.62 0.06	89.34 0.56
24					97.51 0.03				100.75 2.01			98.07 0.17

Table 4. % drug release Comparative percentage drug release of marketed formulation and optimized formulation F9

% Drug Release		
Time(hrs)	Marketed tablets	F9
0.5	9.75	22.08
1	15.56	27.06
2	25.06	30.35
4	39.59	36.32
6	51.06	43.44
8	56.73	51.08
10	85.49	54.91
12	95.97	74.34
18		86.51
24		100.53

Table 5. Kinetic study of Carvedilol phosphate

Formulation Code	Zero order	First order	Higuchi	Peppas	
				r^2	n
F1	0.924	0.907	0.958	0.911	0.418
F2	0.644	0.565	0.745	0.593	0.152
F3	0.866	0.789	0.874	0.746	0.265
F4	0.869	0.840	0.887	0.801	0.278
F5	0.965	0.868	0.911	0.899	0.537
F6	0.688	0.645	0.799	0.711	0.197
F7	0.781	0.0.685	0.847	0.773	0.234
F8	0.862	0.892	0.935	0.920	0.324
F9	0.934	0.932	0.968	0.933	0.389
F10	0.745	0.856	0.871	0.846	0.198
F11	0.973	0.838	0.926	0.913	0.462
F12	0.969	0.819	0.811	0.946	0.717

Conclusion

The present study demonstrated that hydrophilic polymers cellulose esters (HPMC K 100M.SCMC) and natural polymers (guar gum) could be successfully employed for formulating sustained release matrix tablets of Carvedilol phosphate. Among the hydrophilic matrix formers, the rate of drug release was in the following orders Guar gum>HPMCK100M>SCMC. The release rate was almost similar for guar gum, SCMC and HPMC K100m upto 24 hrs. Among all formulation showed the maximum release upto 24 hrs and it is selected as the best formulation.

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