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FORMULATION DEVELOPMENT AND IN VITRO EVALUATION OF CARVIDILOL IMMEDIATE RELEASE TABLETS

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ABSTRACT

The aim of the present study was to develop and optimize immediate release tablets of model drug (Carvedilol) to give quick onset of action with better patient compliance. In such cases, bioavailability of drug is significantly greater and adverse event is reduced than those observed from conventional tablet dosage form. By performing compatibility studies by IR spectrophotometry, no interaction was confirmed. Immediate release tablets were formulated by direct compression method and evaluated by UV-Visibile spectrophotometer. Standard calibration curve prepared to determine the drug content in the prepared tablets. Prior to compression, the blend of drug and excipients were evaluated for flow properties such as Angle of repose, Bulk density, Tapped density, % Compressibility, and Hausner ratio. All the formulation showed excellent properties. Immediate release tablets were prepared by direct compression technique using CADMACH 16 station tablet punching machine, equipped with round flat punches of 8 mm diameter. Post compression evaluation of prepared oral disintegrating tablets were carried out with the help of different pharmacopoeial and non-pharmacopoeial (industry specified) tests. The shape and color of all the formulations were found to be circular and white in color. The thickness was found to be uniform in specific formulations. The hardness and friability are also within the permitted limits. Dissolution of tablets was carried out. The croscaramellose sodium used formulation gave the more dissolution profile compared to other superdisintegrants.

KEY WORDS: Carvedilol, immediate release tablets, croscaramellose sodium

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INTRODUCTION

The need for new oral drug delivery system continues, due to poor patient acceptance for invasive methods, need for exploration of new market for drugs and coupled with high cost of disease management. Developing new drug delivery techniques and utilizing them in product development is critical for pharmaceutical companies to survive this century.

An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques (1)

Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities.

Direct Compression (2-4)

The term direct compression is used to define the process by which tablets are compressed directly from powder blends of the active ingredient and suitable excipients which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation procedures is necessary. The manufacture of tablets using wet granulation or dry granulation methods is both time-consuming and potentially costly. The mechanisms of particle–particle interactions in tablets produced by direct compression are similar to those operative in tablets produced by dry granulation. The advent of direct compression was made possible by the commercial availability of directly compressible tablet vehicles that possess both fluidity and compressibility. The simplicity of the direct-compression process is obvious. But direct compression should not be conceived as a simplified modification of the granulation process for making tablets. It requires a new and critical approach to the selection of raw materials, flow properties of powder blends and effects of formulation variables on compressibility. During the wet granulation process the original properties of the raw materials are, to a great extent, completely modified. As a result, a new raw material is what is finally subjected to compression. Many inadequacies in the raw materials are covered up during the granulation step. This is not true in direct compression and therefore the properties of each and every raw material and the process by which these materials are blended become extremely critical. Direct compression is often preferred because of its simplicity and relatively low cost, but may not always be technically feasible. It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets. The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression.

Wet granulation (5)

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems.

Dry Granulation (5)

Dry granulation processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates). This process is often used when the product to be granulated is sensitive to moisture and heat. Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation equipment offers a wide range of pressures to attain proper densification and granule formation. It is simpler than wet granulation, therefore the cost is reduced. However, this method often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may need to be added to the formulation to facilitate the formation of granules. At last powdered lubricants are added.Carvedilol is indicated in the management of congestive heart failure (CHF), as an adjunct to conventional treatments (ACE inhibitors and diuretics). The use of carvedilol has been shown to provide additional morbidity and mortality benefits in severe CHF. Carvedilol is rapidly and extensively absorbed following oral administration. The absolute bioavailability of carvedilol is approximately 25%.

Plasma levels peak approximately one hour after an oral dose. Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R (+)-carvedilol approximately two to fourfold higher than S(-)-carvedilol following oral administration in healthy subjects. Greater than 98% of carvedilol is bound to plasma proteins, primarily albumin. Carvedilol is highly lipophilic; the volume of distribution is approximately 2 L/kg and is increased in patients with liver disease. After oral administration, the elimination half-life of carvedilol is approximately six to ten hours. Plasma clearance ranges from 500 to 700 mL/minute. Elimination is mainly biliary, with the primary route of excretion being via the faeces. A minor portion is eliminated via the kidneys. The pharmacokinetics of carvedilol are affected by age. Area under the curve (AUC) and Tmax values are increased in the elderly. Plasma levels of carvedilol are approximately 50% higher in the elderly compared to young subjects. Steady-state plasma concentrations of both carvedilol enantiomers increased proportionally over the 6.25 to 50 mg dose range in patients with congestive heart failure. Compared to healthy subjects, congestive heart failure patients had increased mean AUC and Cmax values for both carvedilol enantiomers with up to 50 to 100% higher values observed in class IV patients. The mean apparent terminal elimination halflife for carvedilol was similar to that observed in healthy subjects (6).

To formulate and evaluate tablets Carvedilol (6.25mg) using different superdisintegrants, other excipients and selecting best of them.

MATERIALS AND METHODS

API characterization (7-10)

Organoleptic evaluation

Organoleptic characters like color, odor, and taste of drug were observed and recorded using descriptive terminology.

Calibration Curve of Carvedilol in 0.1N HCL

Preparation of Stock solution

Stock I: 100mg of the drug was accurately weighed and transferred into the 100 ml volumetric flask. It was dissolved in sufficient quantity of buffer and volume was made up to the mark with 0.1N Hcl to get a 1000 µg/ml solution. This was the standard stock solution containing 1 mg/ml of model drug. (Stock I).

Stock 2: From above stock 1 solution 10ml was taken and make up with 0.1N Hcl to 100ml and this was 100ppm concentration solution.

Preparation of the calibration curve

From the stock II solution proper dilutions were made to 10 ml volumetric flasks and were diluted with 0.1N Hcl up to the mark to obtain concentration of 1,2, 3, 4 and 5µg/ml respectively. Absorbance of each solution was measured at 243 nm. The Standard curve preparation was performed. The absorbances on x-axis were plotted against the concentrations on y-axis and r^2 value was obtained.

Pre-Formulation Studies (7-10) FT-1R Studies

The IR absorption spectra of the carvedilol drug and with different superdisintegrants, natural gums and excipients were taken in the range of 4000-450 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powdered and dried potassium bromide .These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due presence super disintegrants and excipients.

Formulation Planning

Immediate Release tablets containing 6.25mg of carvedilol were prepared with a total tablet weight of 150mg. By conducting the thorough literature survey, the excipients were selected and an attempt was made to produce Immediate Release tablets.

General formula

Different superdisintegrants croscarmellose sodium, crospovidone, in the concentration range of 3- 7.5%.. Microcrystalline cellulose (Avicel PH102) was selected as the filler or diluent, owing to its multiple functionalities as binder, disintegrant, compressibility and flowability. Out of the various grades available, the granular form - Avicel PH102 was selected for direct compression purpose, because it had been already reported to provide lower crushing strengths and shorter disintegration times. To improve flow property of the blend magnesium stearate (1.5%) and aerosil (1%) as glidant and lubricant were incorporated, magnesium stearate also decreases the hardness of tablets without affecting the disintegration time.

Formulation of different batches

The main aim of the present study was to formulate different batches using three various superdisintegrants and other ingredients in varying concentrations. So, different batches of formulations were planned accordingly shown in table-1. According to that F1, F2, F3 (with Crospovidone-3%, 5%, and 7.5%), F4, F5, F6 (with Crosscaramellose-3%, 5%, 7.5%).

Table-1 Formulations of Different Batches (F1-F6)

	Formulations Code					
Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Carvedilol	6.25	6.25	6.25	6.25	6.25	6.25
Crospovidone	4.5	7.5	11.25	------	------	-------
Croscarmellose sod.	------	------	------	4.5	7.5	11.25
MCC 102	qs	qs	qs	qs	qs	qs
Magnesium stearate	2.25	2.25	2.25	2.25	2.25	2.25
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5
Total tablet weight	**150mg**	**150mg**	**150mg**	**150 mg**	**150mg**	**150mg**

Direct compression method

The model drug (carvedilol) is thoroughly mixed with the super disintegrants and then other excipients are added to the mixer and passed through the sieve (sieve no. 40). Collected the powder mixer, blended with magnesium stearate (pre sieved through sieve no. 60), the powder blend is subjected to drying for removal of moisture content and then subjected the blend for tablet compression by using Round and flat faced punches in CADMACH 16 punches tablet punching machine. Punches of 8 mm diameter were used for compression. Tablet of 150 mg was prepared by adjusting hardness and volume screw of compression machine properly.

RESULTS AND DISCUSSION

API Characterization

Organoleptic properties

Organoleptic properties such as color was evaluated and the results are within the standards, shown in (Table-2).

Table-2 Organoleptic characteristics of the drug

Characteristics	**Results**
Colour	White to off white powder

Analytical evaluation (Determination of λ_{max})

The absorption wavelength maximum was found to be at 243 nm.

Pre-Formulation Studies

FTIR spectral data

The FT-IR represents the peaks of the carvedilol functional groups. These peaks were not affected, they were prominently observed in IR-spectra of carvedilol along with super disintegrants, simple disintegrants and other excipients. There was no difference in the position of the absorption bands, hence providing evidence for the absence of any chemical incompatibility between pure drugs with the excipients.

Pre- Compression Parameters

Angle of repose

All the formulations prepared by direct compression method showed the angle of repose less than 25, which reveals excellent flow property.

Bulk density, Tapped density, Hausner ratio, Compressibility index

The bulk density and tapped density for all formulation (F1 – F6) varied from 0.35 - 0.45 gm/cm^3 and 0.41 - 0.51 gm/cm^3 respectively. The results of carr's consolidate index or % compressibility index and hausner's ratio for the entire formulation (F1 – F6) blend range from 10.64- 14.63 and 1.12-1.17 respectively, shows fair flow properties. The results are shown in the (Table-3).

Table-3 Evaluation of tablet blend for formulations (F1 – F6)

Formulation	Bulk Density (g/cc)	Tapped Density(g/cc)	Hausner ratio	Compressibility index (%)	Angle of repose
F1	0.42	0.48	1.14	12.50	26.09
F2	0.39	0.45	1.15	13.33	27.16
F3	0.35	0.41	1.17	14.63	25.57
F4	0.44	0.50	1.14	12.00	26.38
F5	0.42	0.47	1.12	10.64	28.94
F6	0.45	0.51	1.13	11.76	24.64

Post Compression Parameters

Hardness test

By using the superdisintegrants, the hardness values ranged from 3.0-3.6 kg/cm^2 for formulations (F1-F6) and were given in (Table-4).

Weight variation test

The entire tablet passes weight variation test, as the average % weight variation was within the Pharmacopeial limit - 7.5%. It was found to be 148mg -151 mg. The weight of all the tablets was found to be uniform with less deviation (Table-4).

Friability test

The friability values were found to be within the limit 0.32-0.40 (0.5 - 1%). The above evaluation parameter showed no significant difference between F1-F6 formulations(Table-4).

Table-4 Evaluation of Immediate Release Tablets for formulations (F1 – F6)

Formulation	Hardness(kg/cm^2)	Friability (%)	Weight (mg)	Thickness(mm)
F1	3.2	0.35	151	2.20
F2	3.0	0.32	148	2.21
F3	3.4	0.36	150	2.16
F4	3.6	0.34	151	2.11
F5	3.2	0.38	150	2.19
F6	3.5	0.40	148	2.13

In-vitro **Disintegration test**

Disintegration test carried out in modified dissolution apparatus, Results shows The disintegration time of F1, F2, F3 with 3%, 5%, 7.5% CP formulations is 17, 14, 10 sec respectively and is almost better than F4, F5, F6, formulations (Table-5), and comparative profile (Figure-1 and 2).

Table-5 Evaluation of Immediate Release Tablets for formulations (F1 – F6)

Formulation	Disintegration time(sec)	Drug content (%)
F1	17	97.80
F2	14	99.05
F3	10	98.12
F4	25	99.10
F5	20	99.48
F6	15	98.16

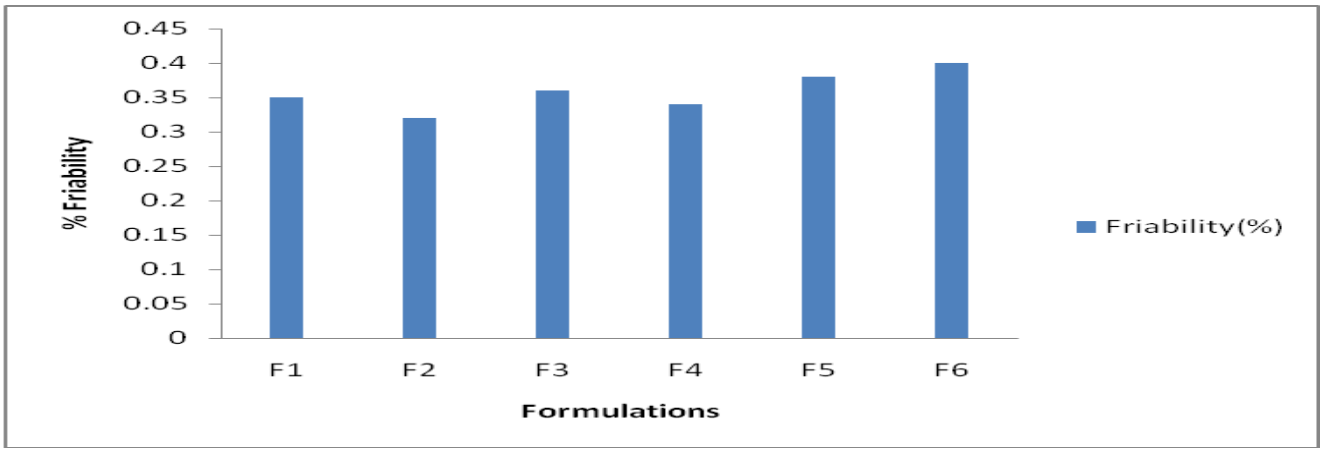

Figure-1 Bar graph comparison friability for formulations (F1- F6)

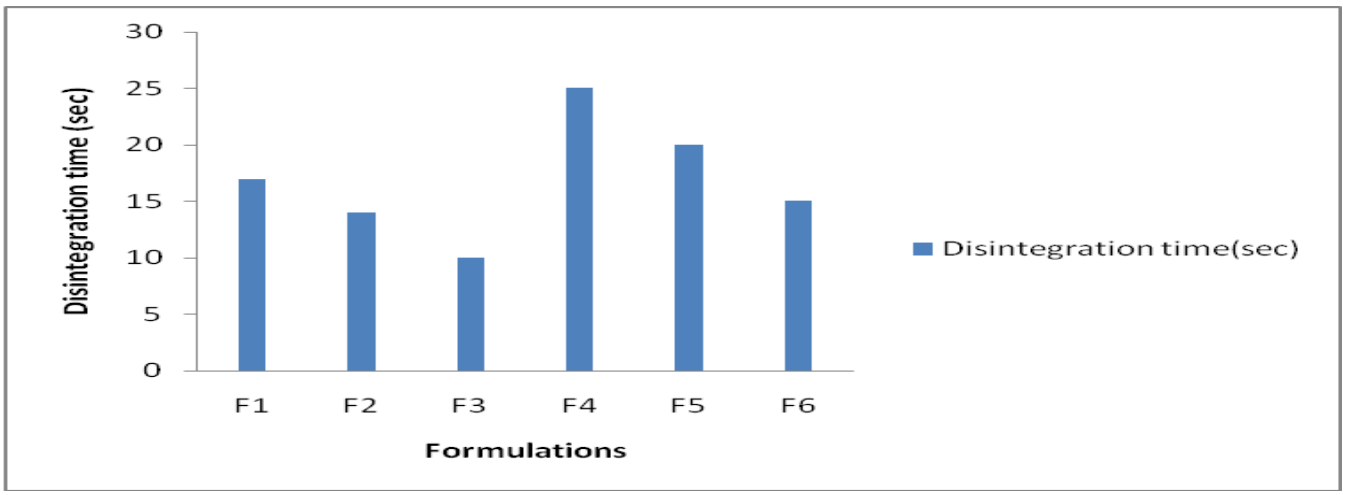

Figure-2 Bar graph comparison between Disintegration times for formulations (F1- F6)

In-vitro **Dissolution studies**

Dissolution is carried out in USP apparatus type-2 apparatus at 50rpm in 900ml dissolution media (0.1N HCL) for 60 minutes. At the end of 30 minutes almost total amount of the drug is released (i.e. 99%), from the formulation prepared by the direct compression method with 7.5% croscaramellose sodium (Table-6, Fig-3 and 4).

Table-6 Cumulative % drug release for formulations (F1 – F6)

Time in min	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	19	21	13	21	33	39
10	32	34	22	45	54	56
15	40	45	52	52	63	75
30	51	53	76	63	70	98
45	67	70	99	75	92	-
60	80	94		88	99	-

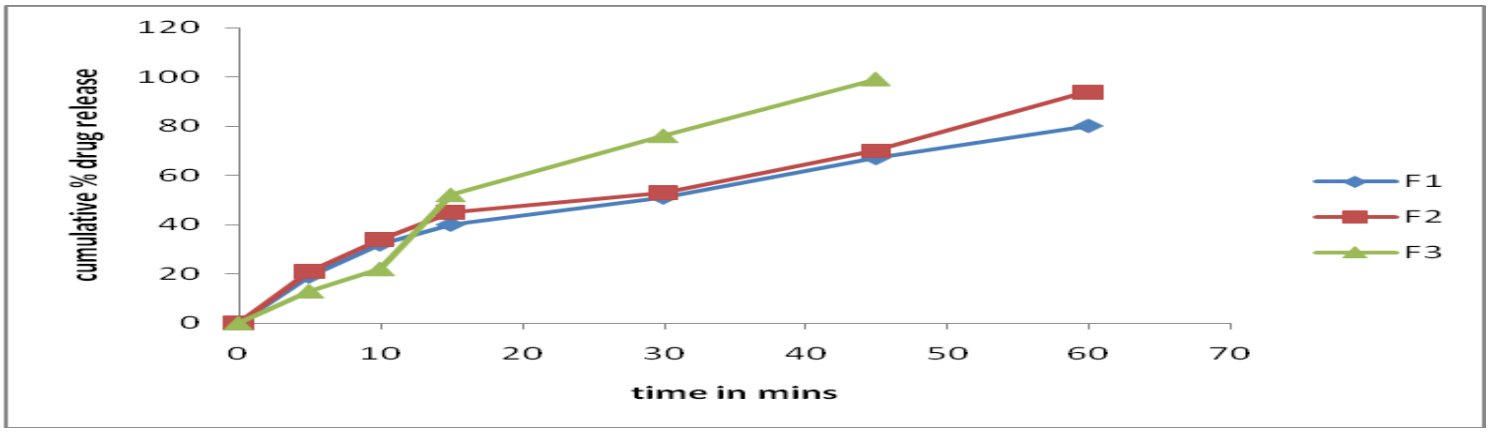

Figure-3 Linear graph comparison between cumulative % drug release for formulations (F1- F3)

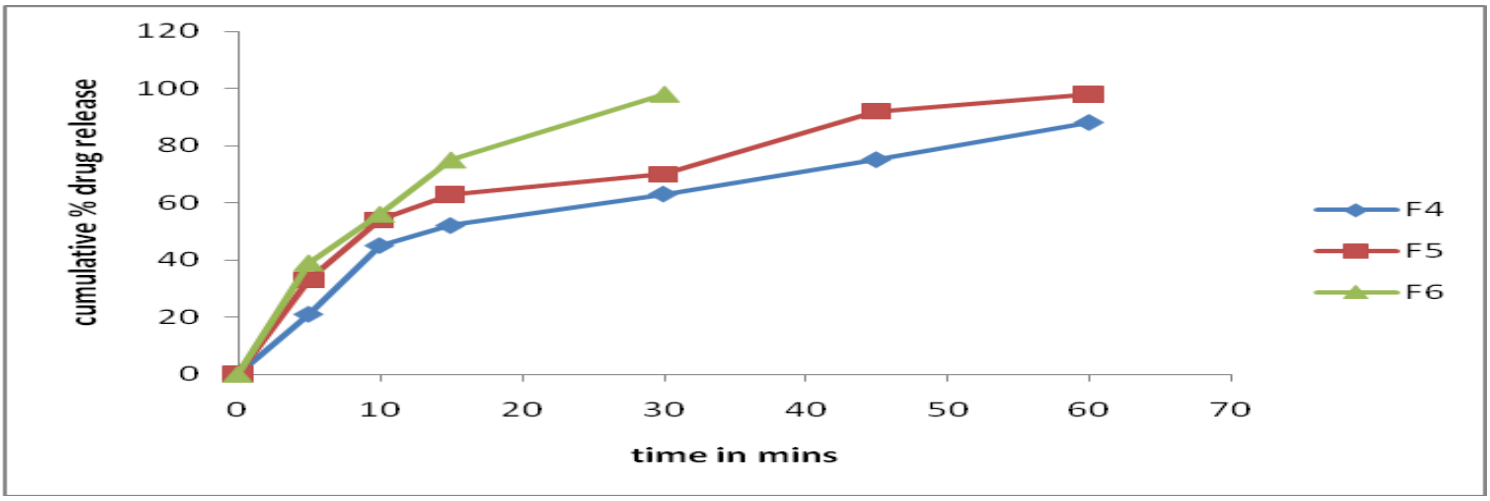

Figure-4 Linear graph comparison between cumulative % drug release for formulations (F4 - F6

CONCLUSION

The above results suggest that the formulated immediate release tablets of Carvedilol exhibited good physical parameters. The overall results indicated that formulation F5 with croscaramellose (7.5%) had a higher edge compared to other formulations containing superdisintegrants. They satisfy all the criteria for immediate release tablets. This direct compression process is simple, reproducible and robust to prepare immediate release tablets of Carvedilol and other anti-hypertensive drugs.

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