

**FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLET OF
CARVEDILOL WITH NATURAL SUPERDISINTEGRANT AND SYNTHETIC
DISINTEGRANTS**Reena Thakur^{1*}, Sunidhi Mahant¹, Shivali Singla¹ and Sachin Goyal¹¹Himalayan Institute of Pharmacy, Kala Amb, H.P.

*Corresponding Author: Reena Thakur

Himalayan Institute of Pharmacy, Kala Amb, H.P.

Article Received on 10/12/2018

Article Revised on 31/12/2018

Article Accepted on 20/01/2019

ABSTRACT

Introduction: 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. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because of their quick onset of action easy administration, economical and better patient compliance. **Methodology:** In present research work the immediate release tablets of Carvedilol were prepared using natural or synthetic superdisintegrants by wet granulation method. At its initial stage preformulation studies were carried out to check physicochemical properties of the drug and compatibility with excipients. Nine formulations were prepared and evaluated for minimum possible disintegrating time to optimize the best formulation. First three of them contain synthetic disintegrant i.e. Croscopolvidone, another three contain natural superdisintegrants, and for last three contain Sodium starch glycolate. All were evaluated at pre and post compression phases also. All the batches, then further evaluated for hardness, thickness, weight variation, drug content uniformity, *In vitro* disintegration time and *In vitro* release studies. **Results and Conclusion:** All the prepared formulations show significant results obtained by Pharmacopoeial quality control test. On the basis of disintegration test observations F3 and F6 formulations were found to be best among all batches.

KEYWORDS: Preformulation, Superdisintegrant, Dissolution Testing, immediate release tablets etc.**1. INTRODUCTION**

An oral dosage form is the physical form of a dose of a chemical compound used as a drug or medication intended for administration or consumption by oral route. Common oral dosage forms are tablets or capsules. Tablets are solid preparations each containing a single dose of one or more active substances with or without excipients usually obtained by compressing uniform volumes of particles.^[1]

Tablets are defined as solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles. They are intended for oral administration, some are swallowed whole, some after being chewed. Some are dissolved or dispersed in water before being administered and some are retained in the mouth, where the active ingredient "liberated".^[2]

Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released from tablet that is dissolved in the fluids of mouth, stomach and intestine and then absorbed into

systemic circulation by which it reaches its site of action.^[3]

Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g. simplicity and economy of preparation, stability and convenience in packing, shipping and dispensing] and the patient [e.g. accuracy of dosage, compactness, portability, blandness of taste and ease of administration].^[4]

Heart failure is a growing problem with an increasing number of affected people and with an increasing burden on society. Much has been done to improve survival in patients with heart failure. The failing human heart has an increased adrenergic drive, which mediates its adverse effect through beta1- and possibly beta2- and alpha1-adrenergic receptors. This was the rationale for introducing beta-blockers in the treatment of chronic heart failure. Beta1-receptors are down-regulated in the failing heart; the beta2-receptors are un-changed and the alpha1-receptors are increased. In patients with heart failure it was found that 50% of the adrenergic receptors

in the heart were beta1-receptors and the rest were beta2- and alpha1-receptors.

Most of the myocardial damage observed in heart failure appears to be beta1-mediated with both pathological hypertrophy as well as apoptosis being mediated via the beta1-receptor. Much myocardial damage in the failing human heart is mediated by norepinephrine (NE). The relative potency of NE for beta1-, beta2-, and alpha1-receptors is 20:1:2. Norepinephrine is released from presynaptic stores and stimulates beta1-receptors preferentially. Carvedilol is a drug which act on alpha as well as on beta.^[5]

Carvedilol, is a beta blocker used for treating mild to severe congestive heart failure (CHF), left ventricular dysfunction (LVD) following heart attack in people who are otherwise stable, and for treating high blood pressure. Beta blockers block the beta receptors on heart muscle and other cells, making them more relaxed and less responsive to stress hormones. Carvedilol also blocks alpha receptors, which are found on blood vessels, and relaxes the blood vessels, dilating them, which lowers blood pressure and vascular resistance. It is a non-

selective beta blocker and belongs to the third generation of beta blockers.^[6,7]

In the present research immediate release tablets of carvedilol were prepared by using natural superdisintegrant and synthetic disintegrants that facilitate disintegration and disaggregation are usually included in immediate release solid dosage forms.

2. MATERIAL AND METHOD

Carvedilol was obtained as a complimentary sample by Alkempvt. Ltd. Baddi India. Microcrystalline cellulose 102, Cross povidone, Talc, Sodium starch glycolate, Aerosil and magnesium stearate was received from Acme Pvt. Ltd. Baddi India. Fenugreek seed mucilage was buying from Local Market, Kala Amb.

2.1 Method

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

2.1.1 Formulations of Different Batches (F1-F9) (Table 1)

Table 1: Formula of Different Batches F1-F9.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carvedilol	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Crospovidone	3	5	7.5	-	-	-	-	-	-
Fenugreek seeds mucilage	-	-	-	3	5	7.5	-	-	-
SSG (Sodium starch glycolate)	-	-	-	-	-	-	3	5	7.5
MCC 102	qs	qs	qs	qs	qs	qs	qs	qs	qs
Magnesium stearate	2.25	2.25	2.25	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	1.5	1.5	1.5

The immediate release tablets of carvedilol were prepared by wet granulation method by using were different batches of various superdisintegrants and other ingredients in varying concentrations as shown in Table 1. According to that F1, F2, F3 (with Crospovidone-3%, 5%, 7.5%), F4, F5, F6 (with Fenugreek seeds mucilage-3%, 5%, 7.5%), F7, F8, F9 (with Sodium starch glycolate-3%, 5%, 7.5%) were formulated. Micro crystalline cellulose was used as a binder. The wet mass was granulated using sieve no. 12 and the granules formed were dried in a dryer at 40°C for 30 minutes. The prepared granules were further blended with remaining quantity of superdisintegrants. At last purified talc and magnesium stearate were added and compressed into tablets.^[8]

3. Preformulation studies

The major purpose of pre-formulation is rationale development of safe and effective dosage form. It is the process of optimizing the delivery of drug through determination of physico-chemical properties of compound that could affect the presentation and

development of an efficient dosage form. Various pre-formulation studies were carried out.

3.1 Organoleptic evaluation of Pure drug^[9]

Organoleptic characters like colour, odour, and taste of drug were observed and recorded using descriptive terminology.

3.2 FT-IR Studies.^[10,11,12]

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 to the presence of super disintegrant and excipients.

3.3 Angle of repose

A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

$$\tan \theta = h/r$$

3.4 Bulk density and tapped density.^[13]

Apparent Bulk density (gm/ml) of the drug was determined by pouring (pre sieved 40-mesh) gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. Then after pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density was calculated by following formula.

Bulk density= Mass of a powder/Bulk volume

Tapped density the drug was determined by pouring gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. In USP Tap Density Tester, Tap density is measured in 500taps, 750 taps & 1250taps with drop/time-(299-302). Volume occupied by the sample after tapping were recorded and tapped density was calculated.

Tapped density= Fluff Density-Tapped density/Tapped density \times 100

3.5 Measurement of Powder Compressibility (Carr's compressibility index)

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. High density powders tend to possess free flowing properties. A useful empirical guide is given by the Carr's index or compressibility index calculated from bulk density and tapped density.

3.6 Hausner ratio^[14]

Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value of indicates better flow and vice versa.

Hausner ratio = tapped density-fluff density/tapped density

4. Evaluation parameters of tablets.^[15-18]

4.1. Organoleptic properties

Organoleptic properties such as taste, colour, odour, were evaluated. Ten tablets from each batch were randomly selected and tested for taste, colour, odour and physical appearance.

4.2. Uniformity of Thickness

The thickness of individual tablets of 6 numbers were measured with vernier callipers, it permits accurate measurements and provides information of the variation between tablets. Tablet thickness should be controlled within $\pm 5\%$ variation of standard value.

4.3. Hardness

The tablet hardness of different formulations was measured using the Monsanto hardness tester for 6 tablets. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge on the barrel to indicate the force. The force of fracture is recorded and the zero-force reading is deducted from it. Generally, a minimum hardness of 5 - 7 kg/cm² is considered acceptable for uncoated tablets.

4.4. Weight Variation Test

Twenty tablets from each batch were weighed with electronic digital balance and average weight was determined. Then individual tablets were weighed and individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Standard deviation was calculated. Using this procedure weight variation range of all the batches were determined and recorded.

4.5. Friability

The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Thirty-three tablets (6.600gms.) were initially weighed (Initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (final). The percentage friability was then calculated by,

%Friability=Loss in weight/ Initial weight \times 100

4.6. In vitro Disintegration time^[19]

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration apparatus as per I.P. specifications.

I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using 0.1N HCl as dissolution medium maintained at $37\pm 2^\circ\text{C}$ as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the 0.1N HCl maintained at $37\pm 2^\circ\text{C}$. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

4.7. Drug Content Uniformity.^[20-23]

Twenty tablets were selected randomly and powdered. A quantity of this powder corresponding to one tablet was dissolved in 100 ml of 0.1N HCl, stirred for 15 min and filtered. 1 ml of the filtrate was diluted to 100 ml with 0.1N HCl. Absorbance of this solution was measured at 243nm using 0.1N HCl as blank and content of drug was estimated.

Amount of drug released=Absorbance of test/absorbance of standard × strength of standard/strength of test × potency/100m×average weight=mg.

Absorbance of test/absorbance of standard × standard weight /volume of diluents× 5/100× volume of diluents/test weight×100/5× potency of weight/100× average weight=%

4.8. *In vitro* Dissolution studies.^[24]

Dissolution of the tablet of each batch was carried out using USP type II apparatus using paddles at 50 rpm. As per the official recommendation of IP 900ml of 0.1N HCl used as dissolution medium and the temperature of the medium was set at 37 ± 0.5 OC. 5 ml of sample was

withdrawn at predetermined time interval of 5min., 10min., 15min 20min, 30min, 45mins and 60min. And same volume of fresh medium was replaced. The withdrawn samples were analysed by an UV-visible spectrophotometer at 243 nm using 0.1N HCl solution as blank solution.

The drug content was calculated using the equation generated from standard calibration curve. The % cumulative drug release was calculated.

Cumulative %= Amount of drug released/Amount of drug loaded × 100=%age

5. RESULT AND DISCUSSION

5.1 Preformulation studies

5.1.1 Organoleptic properties

The drug was of white colour and it have pungent odour.

5.1.2 Analytical evaluation (Determination of λ_{max})

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

Calibration Curve of Carvedilol with 0.1N HCl [Table 2 & Figure 1]

Table 2: Calibration of Carvedilol.

Sr. no.	Concentration	Absorbance at 243nm	Beer's Lambert range(mg/ml)	Coefficient of regression
1.	0	0	5-35	0.996
2.	1	0.084	5-35	0.996
3.	2	0.165	5-35	0.996
4.	3	0.249	5-35	0.996
5.	4	0.330	5-35	0.996
6.	5	0.445	5-35	0.996

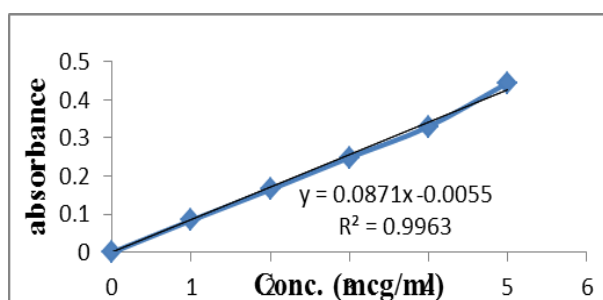


Figure 1: Calibration Curve of Carvedilol with 0.1N HCl.

5.1.3 FT-IR 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 natural super disintegrant and other excipients. The spectral details of the drug and the excipients are shown in (Figure 2, 3). 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.

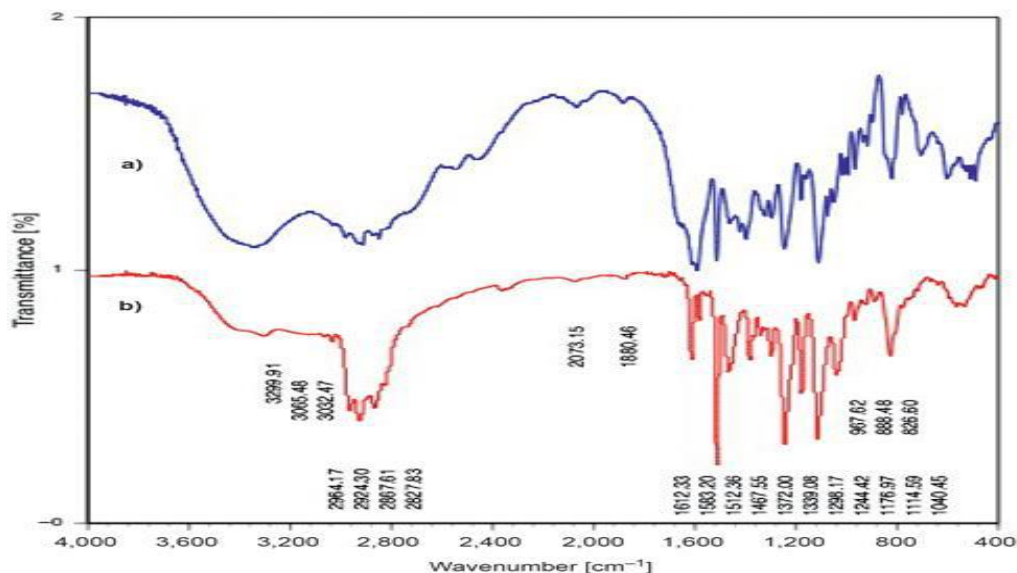


Figure 2: FT-IR spectra of a) Carvedilol: b) Crospovidone.

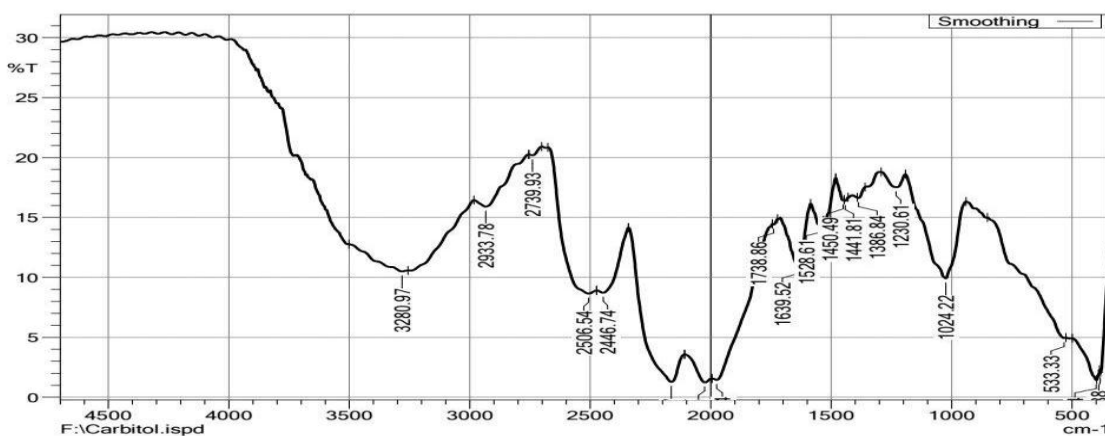


Figure 3: FT-IR spectra of Carvedilol with Fenugreek seed mucilage.

5.1.4 Angle of repose

All the formulations prepared by wet granulation method showed the angle of repose less than 25, which reveals excellent flow property. And F6 showing angle of repose 24.64.(Table 3)

5.1.5 Bulk density, Tapped density, Hausner ratio, Compressibility index of formulations

The bulk density and tapped density for all formulation (F1 – F9) varied from 0.35 - 0.46 gm/cm³ and 0.41 - 0.52 gm/cm³ respectively. The results of car's consolidate index or % compressibility index and Hausner's ratio for the entire formulation (F1 – F9) blend range from 11.11- 14.63 and 1.12-1.17 respectively, shows fair flow properties. The results are shown in table 5.2. F3 and F6 showing all the values in range that indicates that they have excellent properties.(Table 3)

Table 3: Flow Characteristics of F1-F9.

Sr. no.	Formulation	Angle of repose (±SD)	Bulk Density (g/cc)(±SD)	Tapped Density(g/cc)(±SD)	Hausner ratio(±SD)	Compressibility index (%) (±SD)
1.	F1	26.09±0.02	0.42±0.03	0.48±0.04	1.14±0.03	12.50±0.05
2.	F2	27.16±0.04	0.39±0.07	0.45±0.05	1.15±0.04	13.33±0.07
3.	F3	25.57±0.06	0.35±0.02	0.41±0.03	1.17±0.06	14.63±0.03
4.	F4	26.38±0.05	0.39±0.04	0.50±0.04	1.13±0.02	12.00±0.04
5.	F5	28.94±0.07	0.41±0.05	0.47±0.06	1.12±0.03	10.64±0.05
6.	F6	24.64±0.03	0.36±0.03	0.44±0.04	1.13±0.04	11.23±0.06
7.	F7	29.10±0.02	0.38±0.06	0.43±0.02	1.13±0.04	11.63±0.04
8.	F8	27.69±0.04	0.40±0.04	0.45±0.05	1.13±0.03	11.11±0.07
9.	F9	25.18±0.05	0.46±0.05	0.52±0.03	1.13±0.02	11.54±0.05

5.2 Evaluation parameters of tablets

5.2.1. Organoleptic properties

All the tablets show similar colour, odour, taste and physical appearance. There is no impact of natural superdisintegrants in their organoleptic properties.

5.2.2. Hardness test

By using the natural superdisintegrants, the hardness values ranged from 3.0-3.5 kg/cm² for formulations (F1-F9). (Table 4)

5.2.3. 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 - 152 mg. The weight of all the tablets was found to be uniform with less deviation. (Table 4)

5.2.4. Friability test

The friability values were found to be within the limit 0.32-0.41 (0.5 - 1%). The above evaluation parameter showed no significant difference between F1-F9 formulations. (Table 4)

5.2.5. Thickness

By using natural superdisintegrants, the thickness values ranged from 2.11-2.20(mm) for formulations (F1-F9). F3, F4 and F6 showing good result. (Table 4)

Table 4: Evaluation Parameters of the Tablets.

Sr. no.	Formulations	Hardness(kg/cm ²) (Mean ±SD)	Weight (mg)	Friability (%)	Thickness (mm)
1.	F1	3.2±0.2	151	0.35	2.20
2.	F2	3.3±0.3	149	0.34	2.21
3.	F3	3.4±0.2	150	0.36	2.16
4.	F4	3.6±0.3	151	0.34	2.11
5.	F5	3.2±0.2	150	0.37	2.19
6.	F6	3.1±0.4	148	0.33	2.11
7.	F7	3.2±0.3	152	0.37	2.20
8.	F8	3.3±0.2	151	0.38	2.18
9.	F9	3.4±0.3	149	0.40	2.14

5.2.6. In-vitro Disintegration test

Disintegration test carried out in modified dissolution apparatus, Results shows the formulations with 3%, 5%, 7.5% of SSG having high disintegrating time as 32, 24, 20 sec. 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, F7, F8, F9 formulations, and comparative profile. F3 and F6 showing minimum time in disintegration. (Table 5)

5.2.7. Drug content uniformity

The concentration of the drug in all the formulations with natural super-disintegrant was found to be 99.18%. It was within the IP limits. The concentration of drug with Crospovidone was found to be 98.66%. And the concentration of drug with SSG was found to be 97.12%. (Table 5)

5.2.8. In-vitro Dissolution studies

Dissolution is carried out in USP Apparatus Type-II 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. 98%), from the formulation prepared by the wet granulation method with fenugreek seed mucilage. (Table 6) showing the % cumulative drug release.

Table 5: Disintegration Time and Drug content of formulations (F1 – F9).

Formulation	Disintegration time(sec)	Drug content (%)
F1	17	97.80
F2	14	99.05
F3	10	98.12
F4	25	99.10
F5	20	98.18
F6	15	98.16
F7	32	97.45
F8	24	98.16
F9	20	98.19

Table 6: In-vitro Dissolution Profile F1-F9.

Time in min	F1 (Mean \pm SD)	F2 (Mean \pm SD)	F3 (Mean \pm SD)	F4 (Mean \pm SD)	F5 (Mean \pm SD)	F6 (Mean \pm SD)	F7 (Mean \pm SD)	F8 (Mean \pm SD)	F9 (Mean \pm SD)
0	0	0	0	0	0	0	0	0	0
5	19 \pm 0.81	21 \pm 0.89	13 \pm 0.78	21 \pm 0.89	33 \pm 0.80	39 \pm 0.56	28 \pm 0.78	29 \pm 0.76	28 \pm 0.67
10	32 \pm 0.64	34 \pm 0.81	22 \pm 0.57	45 \pm 0.67	54 \pm 0.60	56 \pm 0.67	40 \pm 0.87	43 \pm 0.87	45 \pm 0.78
15	40 \pm 0.73	45 \pm 0.56	52 \pm 0.67	52 \pm 0.61	63 \pm 0.70	75 \pm 0.78	62 \pm 0.66	67 \pm 0.57	60 \pm 0.76
30	51 \pm 0.67	53 \pm 0.89	76 \pm 0.80	63 \pm 0.56	70 \pm 0.56	98 \pm 0.67	74 \pm 0.67	81 \pm 0.87	78 \pm 0.89
45	67 \pm 0.76	70 \pm 0.78	89 \pm 0.78	75 \pm 0.67	92 \pm 0.76	-	83 \pm 0.76	89 \pm 0.65	82 \pm 0.80
60	80 \pm 0.78	94 \pm 0.80	-	88 \pm 0.78	98 \pm 0.75	-	89 \pm 0.87	98 \pm 0.87	99 \pm 0.56

CONCLUSION

From the present research it was concluded that formulated immediate release tablets of Carvedilol with Fenugreek seed mucilage exhibited good physical parameters. The overall results indicated that formulation F6 and F3 with (Fenugreek seed mucilage and Crospovidone) (7.5%) had a higher edge compared to other formulations containing superdisintegrants. They satisfy all the criteria for immediate release tablets. With the progress in the formulation of rapid disintegrating tablets, now it is possible to formulate these tablets with reduced quantity of superdisintegrants. Rapidly disintegrating dosage forms have been effectively commercialized by using numerous types of super disintegrating agents. By the use of many and different types of super disintegrating agent's patient compliance, commercial and therapeutic benefits have enhanced. At a time when researchers are faced with increasing amounts of poorly soluble drugs, it is very important to select super disintegrating agents that maximize drug dissolution. Due to fast acceptance of RDTs by patients and pharmaceutical companies, the market of this dosage form is growing and the product pipeline quickly, but without the field of super disintegrating agents it would not have been possible.

REFERENCES

- Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. Philadelphia: Lea & Febiger, 1976.
- Zisaki A, Miskovic L, Hatzimanikatis V. Antihypertensive drugs metabolism: an update to pharmacokinetic profiles and computational approaches. *Current pharmaceutical design*, 2015 Feb 1; 21(6): 806-22.
- Abdelbary G, Prinderre P, Eouani C, Joachim J, Reynier JP, Piccerelle PH. The preparation of orally disintegrating tablets using a hydrophilic waxy binder. *International journal of pharmaceutics*, 2004 Jul 8; 278(2): 423-33.
- Ghosh T, Ghosh A, Prasad D. A review on new generation orodispersible tablets and its future prospective. *Int j pharm pharm sci.*, 2011 Jan; 3(1): 1-7.
- Pradeep HK. Design and in vitro evaluation of mouth dissolving tablets of venlafaxine hydrochloride (Doctoral dissertation, RGUHS).
- Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *New England Journal of Medicine*, 1998 Nov 12; 339(20): 1415-25.
- Manivannan R. Oral disintegrating tablets: A future compaction. *Drug Invention Today*, 2009 Nov 1; 1(1): 61-5.
- Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, 2004; 21(6).
- Zhao N, Augsburg LL. Functionality comparison of 3 classes of superdisintegrants in promoting aspirin tablet disintegration and dissolution. *AAPS pharmscitech*, 2005 Dec 1; 6(4): E634-40.
- Pahwa R, Piplani M, Garg VK, Rao R, Lamba HS. Formulation and evaluation of orally disintegrating tablets: comparison of natural and synthetic superdisintegrants. *Der Pharmacia Lettre*, 2011; 3(2): 407-18.
- Hu RF, Zhu JB, Peng DY, Tang JH, Zhou A. Optimization of formulation of Fufang Danshen immediate release tablet by colligation score. *Zhongguo Zhongyaozazhi Zhongguozhongyaozazhi China journal of Chinese materia medica*, 2006 Mar; 31(5): 380-2.
- Sekar V, Chellan VR. Immediate release tablets of telmisartan using superdisintegrant-formulation, evaluation and stability studies. *Chemical and Pharmaceutical Bulletin*. 2008 Apr 1; 56(4): 575-7.
- Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *New England Journal of Medicine*, 1996 May 23; 334(21): 1349-55.
- Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET):

- randomised controlled trial. *The Lancet*, 2003 Jul 5; 362(9377): 7-13.
15. Capricorn Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *The Lancet*, 2001 May 5; 357(9266): 1385-90.
 16. Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Bristow MR, Cohn JN, Lukas MA, Young ST, Packer M. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *New England Journal of Medicine*. 2001 May 3; 344(18): 1358-65.
 17. Bala R, Khanna S, Pawar P. Polymers in fast disintegrating tablets—a review. *Asian J Pharm Clin Res*, 2012; 5(2): 8-14.
 18. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L, Ross RD, Pahl E, Blume ED, Dodd DA, Rosenthal DN. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *Jama*, 2007 Sep 12; 298(10): 1171-9.
 19. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright JT, Oakes R, Lukas MA, Anderson KM. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *Jama*, 2004 Nov 10; 292(18): 2227-36.
 20. Gallo RC, Ferreira AP, Castro RE, Cavalheiro ET. Studying the thermal decomposition of carvedilol by coupled TG-FTIR. *Journal of Thermal Analysis and Calorimetry*, 2016 Mar 1; 123(3): 2307-12.
 21. Kumar GS, Shetty AK, Sambaiiah K, Salimath PV. Antidiabetic property of fenugreek seed mucilage and spent turmeric in streptozotocin-induced diabetic rats. *Nutrition research*, 2005 Nov 1; 25(11): 1021-8.
 22. El-Mahdy AR, El-Sebaïy LA. Preliminary studies on the mucilages extracted from Okra fruits, Taro tubers, Jew's mellow leaves and Fenugreek seeds. *Food chemistry*, 1984 Jan 1; 14(4): 237-49.
 23. Sur P, Das M, Gomes A, Vedasiromoni JR, Sahu NP, Banerjee S, Sharma RM, Ganguly DK. *Trigonella foenum-graecum* (fenugreek) seed extract as an antineoplastic agent. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, 2001 May; 15(3): 257-9.
 24. Panda s, tahiliani p, kar a. Inhibition of triiodothyronine production by fenugreek seed extract in mice and rats. *Pharmacological research*, 1999 Nov 1; 40(5): 405-9.