International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 9, Issue 7, 2017

Original Article

DEVELOPMENT AND OPTIMIZATION OF ORODISPERSIBLE TABLETS OF CARVEDILOL BY COMBINATION OF SUPER-DISINTEGRANTS ADDITION AND SUBLIMATION TECHNIQUES

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Received: 14 Apr 2017 Revised and Accepted: 27 May 2017

ABSTRACT

Objective: Objective of the present research work was to prepare orodispersible tablets of carvedilol (CDL) for dysphagic patients.

Methods: Carvedilol, an anti-hypertensive drug, was chosen as a model drug in this study. Orodispersible tablets of carvedilol were prepared using different super-disintegrating agents such as crospovidone, croscarmellose sodium and sodium starch glycolate at different concentrations. The best formulation was selected based on disintegration and dissolution profile that was further taken for sublimation studies using camphor, menthol and thymol. Drug-excipients interaction studies were carried out by fourier transform infra-red (FTIR) spectrophotometer with pure drug sample and optimized formulation.

Results: The orodispersible tablet formulation having 4% croscarmellose sodium disintegrated in 92 sec. Hence this formulation was considered best formulation and taken further for sublimation studies. A formulation containing 10% w/w of menthol showed disintegration time of 16 sec with more than 96.64% drug release within 15 min. Menthol leaves the porous structure as it sublimates from the tablet. This might have contributed to the decrease in disintegration time. Hence, this formulation was considered optimized.

Conclusion: From this study, it can be concluded that orodispersible tablets of carvedilol may prove to be more efficacious in the treatment of hypertension particularly in dysphagic patients.

Keywords: Orodispersible tablets, Super-disintegrants, Sublimation, Carvedilol, Anti-hypertensive

DOI: http://dx.doi.org/10.22159/ijpps.2017v9i7.19161

INTRODUCTION

Dysphagia is a biomechanical disorder considered as a clinical syndrome. It is defined as "an inability to swallow, or a sensation that solids or liquids do not pass easily from the mouth to the stomach" [1, 3]. From many reported studies it has been estimated that over six million adults have dysphagia [1]. It can occur in all age groups, but the prevalence increases with increase in age [1, 3]. Other categories that experience problems using conventional dosage forms include are mentally ill, uncooperative and nauseated patients, those with condition of motion sickness, sudden episodes of allergic attack or coughing [2]. Oral conventional formulations such as tablets, capsules and liquids pose difficulty in swallowing, especially in dysphasic patients [3].

Carvedilol (CDL) is an oral, cardioselective β-receptor blocking agent, primarily used to treat hypertension [4]. It undergoes extensive first-pass hepatic metabolism due to cytochrome P450 2D6 (CYP2D6) enzymes and its oral bioavailability is only 25-35%. Half-life also varies extensively from 7 to 10 h. The recommended daily dose of CDL is 3.125 mg. Depending on the blood pressure (BP) of the patient and tolerance, the dose may be increased slowly to a maximum of up to 25 mg daily [5].

There is a need for the suitable dosage form which addresses low bioavailability of CDL and eases the administration to dysphagic patients. This study tries to address the same by formulating novel oral drug delivery systems of CDL in the form of orodispersible tablets to increase its pharmacokinetic profile and ease administration to dysphagic patients.

In this study, we formulated and evaluated orodispersible tablets (ODTs) containing CDL using a combination of two different approaches namely: super-disintegrants addition and sublimation techniques. The prepared formulations were subjected to both pre and post compression parameters and evaluations including FTIR, carrs' index, the angle of repose, hausner ratio, hardness, friability, disintegration time and dissolution. The ODT formulation was optimized based on disintegration time (DT) and dissolution rate.

MATERIALS AND METHODS

Materials

Carvedilol was obtained as gift sample from chandra labs, Hyderabad, India. Crospovidone (CP), croscarmellose sodium (CCS), sodium starch glycolate (SSG), microcrystalline cellulose (MCC) and mannitol were purchased from SD fine chemicals ltd, Mumbai, India. Sodium lauryl sulphate (SLS) and aspartame were purchased from standard reagents, Hyderabad, India. Magnesium stearate, camphor, menthol, thymol were purchased from ESSEL fine chem., Mumbai, India. All other ingredients used were of analytical reagent grade.

Methods

Formulation of orodispersible tablets

Orodispersible tablets of CDL were prepared by direct compression method. The details of formulation composition are shown in table 1. Carvedilol, equivalent to 12.5 mg was used in total tablet weight of 200 mg. CP, CCS and SSG were used as super-disintegrants, SLS was used as surfactant, mannitol and MCC as diluents, aspartame as a sweetening agent and magnesium stearate as a lubricant. Drug and all the excipients were weighed accurately and passed through sieve #60 and mixed well. This mixture was transferred to a mortar and grounded for around 10-12 min [6]. The resulting mixture was compressed in single punch compression machine using 7 mm flat surface punches. Based on the DT and drug release profile, formulation F8 having 4% of CCS was optimized and further selected for sublimation studies. As shown in table 2, Camphor, menthol and thymol were used as sublimating agents [11]. Prepared tablets were vacuum dried at 60 °C for 24 h to facilitate the sublimation [7].

Evaluation orodispersible tablets

The prepared ODTs were evaluated for various physicochemical parameters. The formulation that was found optimal with super-disintegrants addition technique was further re-formulated using sublimating agents and evaluated.

Table 1: Formulation of orodispersible tablets of carvedilol using super-disintegrating agents

Ingredients (mg)	Formulation code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Carvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
SLS	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Mannitol	50	50	50	50	50	50	50	50	50	50	50	50
CP	2	4	6	8	-	-	-	-	-	-	-	-
CCS	-	-	-	-	2	4	6	8	-	-	-	-
SSG	-	-	-	-	-	-	-	-	2	4	6	8
MCC	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium. stearate	2	2	2	2	2	2	2	2	2	2	2	2

*Total weight of the tablet was 200 mg. CP = Crospovidone, CCS = Croscaramellose sodium, SSG = Sodium starch glycolate, MCC = Microcrystalline cellulose, SLS-sodium lauryl sulphate.

Table 2: Formulation of orodispersible tablets of carvedilol using sublimating agents

Ingredients (mg)	Formulation code											
	C1	C2	C3	C4	M1	M2	M3	M4	T1	T2	T3	T4
Carvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
SLS	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Mannitol	50	50	50	50	50	50	50	50	50	50	50	50
CCS	8	8	8	8	8	8	8	8	8	8	8	8
Camphor	5	10	20	30	-	-	-	-	-	-	-	-
Menthol	-	-	-	-	5	10	20	30	-	-	-	-
Thymol	-	-	-	-	-	-	-	-	5	10	20	30
MCC	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium. stearate	2	2	2	2	2	2	2	2	2	2	2	2

*Total weight of the tablet was 200 mg. CCS = Croscaramellose sodium, MCC = Microcrystalline cellulose, SLS = sodium lauryl sulphate.

Pre and post compression parameters

Pre-compression parameters (bulk and tapped density, carrs' index, hausner ratio, the angle of repose) and post compression parameters (weight variation, hardness, thickness, friability, Moisture uptake) were determined for the tablet blend and compressed tablets respectively as per pharmacopoeial specifications [8, 9, 10, 16].

***In vitro* disintegration time**

For disintegration study, a method reported by Kadria *et al.* was followed (6). Briefly, tablets were placed in a beaker containing 20 ml distilled water at 37±0.5 °C. Time for complete disintegration of the tablet was measured in triplicate and average values were considered for comparison [6, 17].

Drug release studies

In vitro dissolution of the ODTs was studied using USP XXIV Type II dissolution apparatus (Electrolab, Mumbai, India). A paddle stirrer at 100 rpm and 900 ml of pH 6.8 phosphate buffer maintained at 37±0.5 ^{O}C as dissolution medium was used [11]. Aliquots (5 ml each) were withdrawn at specified time intervals (2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25 and 30 min) and replaced with equal volume of fresh medium to maintain the sink condition. The samples were analyzed for drug content using UV-Visible spectrophotometer at 284 nm [12].

FTIR studies

FTIR studies were performed to find any possible drug-excipient interaction by KBr pellet method using Perkin-Elmer spectrophotometer, USA (Model-1615). For this study, pure carvedilol, carvedilol optimized formulations were studied. Drug and excipients (1:1) were prepared and co-ground with KBr. The resultant mixture was subjected to FTIR studies. Scans were performed from 400-4000 cm^{-1} and an average of 40 scans were taken per sample [13, 18].

RESULTS AND DISCUSSION

Pre-compression parameters

Pre-compression parameters were studied for both blends of ODT formulations prepared using super-disintegrants (CP, CCS, SSG) and sublimating agents (camphor, menthol, thymol). Results are shown in table 3 and 4 below. All the formulations shown adequate flow properties.

Table 3: Pre-compression of formulations prepared using different super-disintegrating agents

Formulation code	Bulk density (gm/cc)±SD	Tapped density (gm/cc)±SD	Cars index±SD	Hausner's ratio±SD	Angle of Repose (θ)	Flow property
F1	0.32	0.38	12.85	1.12	32.46 °	Good
F2	0.34	0.37	11.64	1.14	33.34 °	Good
F3	0.34	0.32	12.33	1.12	25.34 °	Excellent
F4	0.33	0.32	13.83	1.24	27.52 °	Excellent
F5	0.43	0.46	11.44	1.14	32.36 °	Good
F6	0.36	0.42	12.52	1.14	32.34 °	Good
F7	0.35	0.41	12.82	1.15	32.56 °	Good
F8	0.32	0.34	13.02	1.03	28.43 °	Excellent
F9	0.33	0.37	14.39	1.15	33.33 °	Good
F10	0.32	0.34	1.51	1.06	27.44 °	Excellent
F11	0.44	0.52	12.60	1.17	34.22 °	Good
F12	0.33	0.34	12.75	1.06	26.48 °	Excellent

n=3

Table 4: Pre-compression parameters of formulation prepared using sublimating agents

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index	Hausner ratio	Angle of repose (θ)	Flow properties
C1	0.36	0.45	12.34	1.12	28.32 °	Good
C2	0.42	0.48	11.22	1.14	29.43 °	Good
C3	0.32	0.34	14.51	1.22	25.43 °	Excellent
C4	0.33	0.32	11.34	1.21	25.22 °	Excellent
M1	0.34	0.32	14.29	1.24	28.35 °	Excellent
M2	0.32	0.36	12.38	1.14	31.45 °	Good
M3	0.34	0.43	14.645	1.16	32.43 °	Good
M4	0.34	0.32	12.29	1.04	26.42 °	Excellent
T1	0.36	0.40	12.47	1.12	32.33 °	Good
T2	0.36	0.42	14.45	1.14	32.52 °	Good
T3	0.36	0.44	12.67	1.12	34.35 °	Good
T4	0.34	0.36	11.40	1.02	27.16 °	Excellent

n=3

Post compression properties

Post compression studies were performed for both ODT formulations prepared using super-disintegrants and sublimating agents. Results are shown in table 5 and 6. From the data, it is evident that DT for ODT reduce significantly (P>0.001), when prepared by a sublimation method.

Disintegration time

Different super-disintegrants were evaluated in the formulation of CDL-ODT. For this purpose, three commonly used super-disintegrants CP, CCS and SSG were used in the formulation of CDL-ODT and evaluated at four different concentrations (1, 2, 3 and 4% w/w). The effect of disintegrant type and their respective concentration is shown in fig. 1. From the fig., it is evident that there is an inverse linear relation between disintegrant concentration used in the formulation and disintegration time. Disintegration time decreased with increase in super-disintegrant concentration.

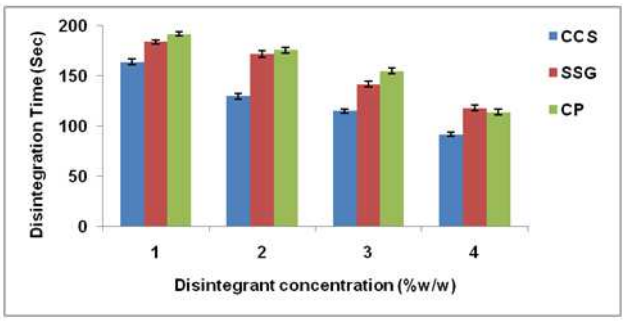

Fig. 1: Comparison of disintegration time of formulations prepared using different super-disintegrants (n=3, Mean=±SD)

Based on the data from fig. 1, it is evident that the disintegration time decreased as the concentration of the super-disintegrants increased. Among all the highest concentrations of disintegrants (4 % w/w), the formulations containing CCS showed lowest mean disintegration time (92±2 sec, *n* = 3) compared to formulations with CP (114±3 sec, *n* = 3) and SSG (118±3 sec, *n* = 3). It is interesting to note that the DT of the SSG at 4% w/w concentration increased more than CP and CCS.

This may be due to the swell and burst mechanism of disintegration in SSG versus wicking mechanisms in CCS and CP. We understand from the literature that an increase in the concentration of SSG leads to gel-like matrix and this might have hindered disintegration of SSG containing formulation [14]. Therefore, based on this data, the CCS containing formulation was selected for further optimization to achieve a target DT below 30 sec using sublimation technique [15].

In sublimation technique, formulations containing 4 % w/w CCS (F8) was re-formulated using commonly used sublimating agents camphor, menthol and thymol at four different concentrations (2.5, 5, 10 and 15% w/w) and disintegration time was noted (table 6). It was observed that, with increasing concentration of the sublimating agent, there was a linear decrease in disintegration time (r^2=0.942). This decrease could be due to the formation of a porous matrix structure in the tablet. The formulation containing 15 %w/w menthol (M4) showed lowest disintegration time (14 sec) but failed in the friability test (1.86%). A formulation containing 10% w/w of menthol (M3) disintegrated within 16 sec and passed the disintegration test. This formulation (M3) showed drug release of 96.64 % within 15 min. Therefore formulation M3 was considered optimized. The comparison of best-selected formulations of super disintegrant addition and sublimation technique is shown in fig. 2.

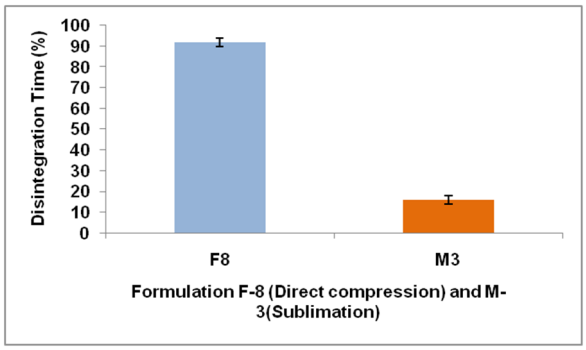

Fig. 2: Comparison of disintegration time of formulations prepared using super-disintegrant (F8) by direct compression and using sublimating agent (M3). (n=3, mean±SD)

FTIR studies

FTIR studies were performed on pure CDL, formulation F8 and optimized formulation (M3). All characteristic peaks of CDL were present in their original positions, denoting the absence of drug-excipient interaction. The FTIR spectra are given in fig. 3.

Drug dissolution studies

In vitro drug release data is presented in fig. 4. From the figure, it is evident that the CDL-ODT formulation (F8) containing 4 % w/w CCS dissolved to an extent of 96.65 % within 20 min. The optimized formulation (M3) containing 10 % w/w of menthol (with 4 % w/w CCS) released 96.64 % of drug within 15 min. The available data was subjected to various mathematical models. The best fit model was found to be first order. The "r^2"value was found to be 0.9882. Analysis using Korsmeyer-Peppas equation gave "r^2" value of 0.9924. The value of "n" was found to be 0.46 indicating the drug release followed non-fickian mechanism of drug release. Drug release from the ODT dosage form was by both diffusion as well as dissolution.

Table 5: Post-compression properties of odts prepared using super-disintegrating agents

Parameters	Formulation code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Weight variation (mg)***	197±2	201±2	202±3	200±3	199±2	196±3	200±2	202±3	199±2	198±3	199±2	201±3
Hardness (kg/cm²)*	5.6±0.2	5.7±0.3	5.8±0.3	5.9±0.2	5.8±0.3	5.2±0.3	5.2±0.3	5.6±0.4	5.8±0.2	6.0±0.2	6.2±0.4	6.2±0.2
Thickness (cm)	3.36±0.6	3.34±0.12	3.36±0.08	3.38±0.4	3.40±0.06	3.32±0.1	3.33±0.06	3.33±0.06	3.31±0.1	3.4±0.08	3.4±0.08	3.38±0.1
Friability (%)*	0.2±20	0.26±0.1	0.7±0.01	0.25±00	0.26±0.01	0.42±0.02	0.26±0.02	0.28±0.03	0.26±0.02	0.35±0.02	0.24±0.02	0.36±0.02
Disintegration time (sec)**	192±2	176±3	155±3	114±3	164±3	130±3	115±2	92±2	184±2	172±3	142±3	118±3

Value are expressed as mean±SD,****n*=[20],***n*=6,**n*=3

Table 6: Post-compression parameters of odt prepared using sublimating agents after drying

Parameters	Formulation code											
	C1	C2	C3	C4	M1	M2	M3	M4	T1	T2	T3	T4
Weight variation (mg)***	194±2	188±2	182±2	167±3	188±4	184±2	175±3	172±4	188±3	182±2	172±4	166±3
Hardness (kg/cm²)*	4.5±0.3	4.6±0.2	4.4±0.3	3.9±0.2	4.4±0.2	4.6±0.3	4.3±0.3	3.9±0.2	4.4±0.3	4.1±0.2	3.8±0.3	3.5±0.2
Thickness (cm)	3.24±0.12	3.26±0.08	3.36±0.22	3.36±0.06	3.26±0.06	3.37±0.1	3.32±0.1	3.36±0.04	3.46±0.08	3.38±0.08	3.28±0.22	3.40±0.1
Friability (%)*	0.41±0.1	0.40±0.22	0.56±0.14	0.85±0.02	0.52±0.08	0.76±0.07	0.92±0.54	1.86±0.12	0.54±0.10	0.58±0.10	0.65±0.14	1.7±0.12
Disintegration time (sec)**	50±2	32±4	24±4	18±4	44±2	24±2	16±2	14±2	62±4	46±5	25±4	17±3

All the values are presented as mean±SD.***n=[20],**n=6,*n=3

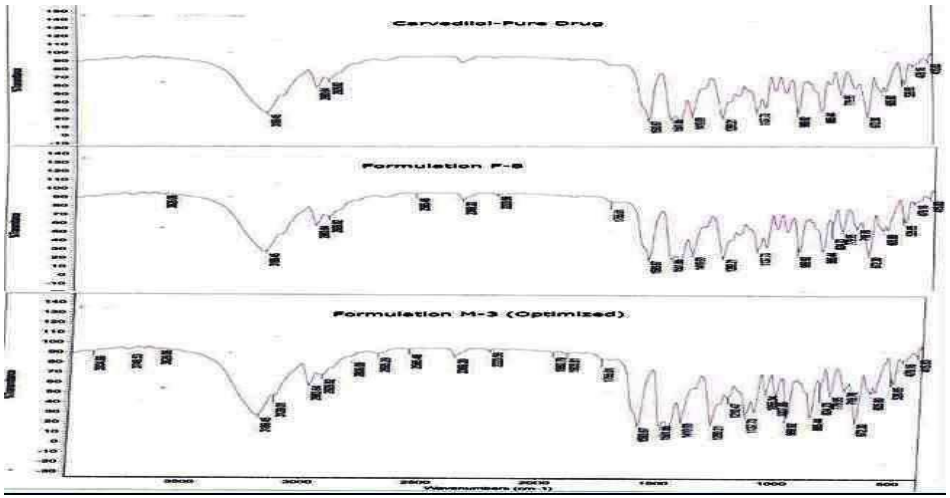

Fig. 3: IR-Spectrum of pure CDL; formulation F8 and Optimized ODT formulation (M3). Scans were performed from 400-4000 cm^{-1}. Average of 40 scans was taken

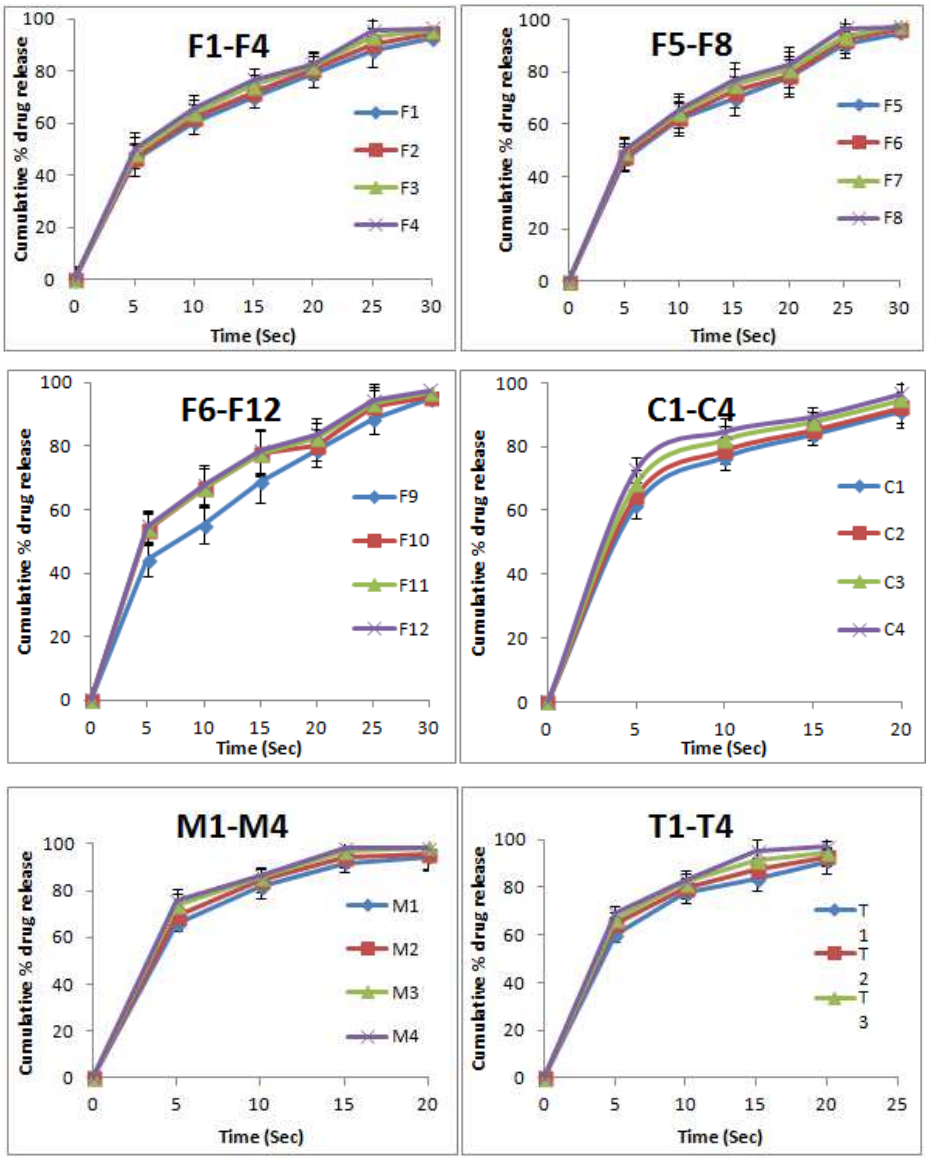

Fig. 4: *In vitro* drug release profile in pH 6.8 buffer for CDL-ODT formulations containing super-disintegrant F1-F12 and sublimating agents Camphor (C1-C4); Menthol (M1-M4); Thymol (T1-T4). (n=3, mean±SD)

CONCLUSION

In this research work, we have made systematic efforts to formulate orodispersible tablets of Carvedilol using different super-disintegrating agents and sublimating agents. Based upon the DT, the formulation containing 4% CCS (F8) was selected for sublimation studies. Formulation M3 containing menthol as sublimating agent showed lowest DT and passed friability test. Hence, formulation M3 was considered optimized. Therefore, from this study, it can be concluded that orodispersible tablets of carvedilol may prove to be more efficacious in the treatment of hypertension particularly in dysphagic patients.

ACKNOWLEDGEMENT

The authors are thankful to Sri Venkateshwara College of Pharmacy, Madhapur, Hyderabad, for constant support and encouragement to complete this research work.

AUTHORS CONTRIBUTION

Dr Vijayanand P performed the practical work. Dr Sridevi P assisted in the preparation of the manuscript. Dr. M Bhagavan Raju supervised the research work.

CONFLICTS OF INTERESTS

All authors have none to declare

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How to cite this article

- Vijayanand P, Sridevi P, Bhagavan Raju M. Development and optimization of orodispersible tablets of carvedilol by a combination of super-disintegrants addition and sublimation techniques. Int J Pharm Pharm Sci 2017;9(7):155-160.