Original Research Article

Formulation and evaluation of carvedilol melt-in-mouth tablet using mucoadhesive polymer and PEG-6-stearate as hydrophilic waxy binder

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Abstract

Purpose: The demand for melt-in-mouth tablets (MMTs) has been rapidly growing during the last decade, especially for the elderly and children who have swallowing difficulties, to avoid first-pass metabolism and quick drug entry into the systemic circulation. **Materials and Methods:** In this work, a new approach has been tried to prepare MMTs using a hydrophilic waxy binder [polyethylene glycol (PEG)-6-stearate]. Carvedilol MMTs were prepared by direct compression method using different mucoadhesive polymers such as hydroxypropyl methylcellulose (HPMC), chitosan, and sodium carboxymethyl cellulose (Na-CMC) at various concentrations (range: 0.5–5%) to reduce the flushing action of saliva and to increase mucosal absorption. All the formulations were evaluated for various physiochemical parameters, and the formulations containing the maximum amount of polymer (F4, F7, and F10) were selected for further stability study. **Results:** The deaggregation time of the tablets was found to be rapid, and the dissolution test revealed that carvedilol was dissolved from the formulation within the compendia limits. This data confirmed that the polymer concentration (0.5–5%) was within acceptable limits. It was also concluded that avicel PH101, pearlitol SD 200, and croscarmellose sodium (CCS) were the appropriate excipients and formulated in the right proportion. **Conclusion:** As a result, mouth dissolving administration of carvedilol formulated with appropriate excipients and especially with chitosan seems a promising alternative to traditional routes.

Key words: Carvedilol, croscarmellose sodium, melt-in-mouth tablet, pearlitol SD 200

INTRODUCTION

Many technologies have come up for fast-dissolving tablets, namely, Zydis, Orasolv, Durasolv, Flashtab, and Wowtab. Technologies like Zydis® and Flashtab have yielded tablets with a very low disintegration time but poor mechanical strength. On the other hand, techniques like Orasolv and Durasolv have resulted in products with sufficient mechanical strength but a comparatively longer disintegration time.[1]

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Melt-in-mouth tablets (MMT) can offer an attractive alternative route of administration. The advantage of the MMT is that the drug can be directly absorbed into the systemic circulation bypassing enzyme degradation in the gut and liver site. In addition, the thin sublingual mucosa, buccal site, and abundance of blood supply in the mouth cavity allow excellent penetration (absorption) of the drug to achieve high plasma drug concentration with a rapid onset of action. Moreover, many patients have difficulty in swallowing tablets and hard gelatine capsules; consequently, they do not take medication as prescribed.[2] For this reason, the development of MMT is a topic of interest for researchers and manufacturers. The main problem associated with MMT is that the patient cannot retain the drug liquid, does tend to swallow liquids; so, there is rapid elimination of the drug due to the flushing action of saliva into the gastrointestinal tract.[3] To increase the intimate contact of MMT with the sublingual mucosa and buccal site, there is a need for adhesion of the tablet to the moist surface of the mucosa and to resist the flushing action of saliva.[4] To overcome this problem, mucoadhesive polymers are used in the formulations. The most commonly used polymers include chitosan, carbopols polymers, and cellulose derivatives.[5,6]

Carvedilol is a novel antihypertensive drug. It is used as an add-on or first-line treatment in angina pectoris, congestive heart failure, hypertension, and left ventricular dysfunction. The precise mechanism by which ß-adrenoceptor blockers exert their beneficial actions in patients with heart failure remains unclear. Several possibilities have been proposed, including reduction in heart rate, ß2-adrenoceptor-mediated modulation of catecholamine release, antagonism of the receptor-mediated toxic actions of norepinephrine on the myocardium, and favorable effects on myocardial energetics. MMT reduces the possibility of missing a dose even during travel or other situations where there is no access to water. The present investigation deals with the development of an effective and stable MMT of carvedilol having adequate hardness, low disintegration time, and pleasant taste.[7]

In this study, we have developed carvedilol MMT using different mucoadhesive polymers to determine the optimum concentration of polymer which can be added to MMTs without changing their basic tablet characteristics, especially disintegration and dissolution time profiles.[8] Therefore, developed MMT formulations were evaluated with basic physical tests for the tablets and *in vitro* permeation studies.

MATERIALS AND METHODS

Carvedilol was gifted by the Torrent Research Centre (Ahmedabad, India); chitosan (medium molecular weight), hydroxypropyl methylcellulose (HPMC) K4 M, sodium carboxymethyl cellulose (Na-CMC), croscarmellose sodium (CCS), and polyethylene glycol (PEG)-6-stearate were purchased from Sigma-Aldrich (Mumbai, India). Avicel PH 101 was gifted by Alex Pharmaceuticals Pvt. Ltd. (Sanand, Gujarat, India). Pearlitol SD 200 was purchased from Chemdyes Pvt. Ltd. (Rajkot, Gujarat, India) and aspartame as a sweetening agent and magnesium stearate as a lubricant from Zydus Healthcare Ltd., India.

Formulation of carvedilol-loaded melt-in-mouth

The composition of each formulation is given in Table 1.

Preparation of granules

Table 1 gives an overview of the percent composition of the granules prepared by wet granulation. PEG-6-stearate was used as a hydrophilic waxy binder in the formulation blend. Wet granulation took place in a planetary mixer (Kenwood, United Kingdom), operated with a planetary action to ensure that all the parts of the mixer were thoroughly active. The granulation process was performed, starting with preliminary trials. Carvedilol, pearlitol SD 200, and polymer were first dry blended for five minutes at 60 rpm. The granulating agent (PEG-6-stearate) was added in small quantities under continuous stirring. The formed wet mass was blended for 10 minutes at 100 rpm and dried at 40°C in a dryer for 120 minutes. Finally, the granules were sieved through 1mm mesh in an oscillating calibrator (Erweka type FGS).

Preparation of tablets

Prior to compression, each formulation of granules was dry blended with CCS (cross carmilose sodium) as superdisintegrants, 1.4% aspartame, and 0.4% magnesium stearate for 15 minutes at 50 rpm. A single-punch tableting machine (Korsch, Lyon France), equipped with flat forced punches with a die diameter of 4 mm, was employed to prepare tablets at the rate of 45 tablets per minute.

Determination of physiochemical parameters

Content uniformity, weight variation, thickness, hardness test, and friability

Uniformity of drug content was determined by dissolving the crushed tablets in distilled water and filtered through a 0.45µm filter. The stock solution was diluted with necessary dilutions and was analyzed at 232 nm using a spectrophotometer (Shimazdu 1700 spectrophotometer). A weight variation test was performed by weighing 20 tablets, and weights of the individual tablets were compared with calculated average weights. The thickness of the tablets was measured with a vernier calliper (Microtek, India). Hardness was checked to find the mechanical strength of the tablet. It is also expressed as crushing strength. It is the force required to break the tablet into halves by compression. The crushing strength of the tablet was measured using a Pfizer hardness tester. Friability test was performed to access the effect of friction, shocks, vibration, capping, or breaking (Roche Friabilator). Twenty-five tablets were weighed and placed in the friabilator, which was then operated at 100 rpm. The tablets were dusted and reweighed. The compressed tablets should not lose more than 1% of their weight.[9,10]

Table 1: Composition of melt-in-mouth tablet formulations of carvedilol

Ingredient (mg)	Code of formulations									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Carvedilol	3.125	3.125	3.125	3.125	3.125	3.125	3.125	3.125	3.125	3.125
Croscarmellose sodium	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
PEG-6-stearate	3.65	3.65	3.65	3.65	3.65	3.65	3.65	3.65	3.65	3.65
HPMC	0	1.2	2.4	3.6	0	0	0	0	0	0
Chitosan	0	0	0	0	1.2	2.4	3.6	0	0	0
Na-CMC	0	0	0	0	0	0	0	1.2	2.4	3.6
Pearlitol 200	7.88	6.91	6.80	6.57	6.91	6.80	6.57	6.91	6.80	6.57
Avicel PH 101	62.92	62.23	61.25	59.29	62.23	61.25	59.29	62.23	61.25	59.29
Aspartame	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13	1.13
Magnesium stearate	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33

PEG: Polyethylene glycol, HPMC: Hydroxypropyl methylcellulose Na-CMC: Sodium carboxymethyl cellulose

In vitro deaggregation

In vitro disintegration time was checked by apparatus specified in the United States Pharmacopeial Convention (USP) at 50 rpm. Phosphate buffer pH 6.8, 900 mL was used as the disintegration medium; the temperature of this was maintained at 37 ± 2°C and the time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.[11,12]

In vitro dissolution studies

The formulations were studied for drug dissolution, employing a USP apparatus type II (paddle type) [Electrolab (ETC-11L) tablet dissolution tester] at 50 rpm. Phosphate buffer pH 6.8, 900 mL was used as dissolution medium which was maintained at 37 ± 0.5°C.[13,14]

In vitro permeation study

In vitro permeation studies were carried out using the Franz diffusion cell. The medium used for permeation was phosphate buffer pH 7.4 which was maintained at 37 ± 0.5°C. Cellulose acetate membrane was used as a permeation barrier. Samples were collected at predetermined time intervals (0, 5, 10, 15, 20, 30, 40, 50, 60, 90, and 120 minutes). They were analyzed for drug content with an ultraviolet (UV) spectrophotometer at 232 nm. Three trials of each batch were performed and the average percentage drug release with standard deviation was calculated and recorded. The calibration curve for carvedilol, in the phosphate buffer, was linear from 1 to 8 μg/mL ($r^2 = 0.998$).[15,16]

Wetting time

A piece of tissue paper folded twice was placed in a small petridish (internal diameter: 6.5 cm) containing 6 mL of simulated saliva pH (phosphate buffer 6.8). A tablet was put on the paper and the time required for complete wetting of the tablet was measured. The average time for wetting with standard deviation was recorded. Each trial was performed in triplicate.[17]

Stability studies

Accelerated stability studies were carried out at 30 ± 2°C, 65 ± 5 °RH and 40 ± 2°C, 75 ± 5 °RH for three months. The tablets were evaluated for hardness, variation in weight, friability, loss on drying, disintegration, drug release, and uniformity of content.[18,19]

RESULTS

Determination of physiological parameters

The physiological properties of the MMTs are given in Table 2. Results for uniformity of drug content were found to be the best among different batches of tablets and percentage of drug content was found to be more than 98%. The results have shown a good distribution profile of the drug within the tablets. The weight and thickness of all the formulations ranged from 78.73 to 80.08 mg and from 2.02 to 2.08 mm, respectively. All tablets prepared in this study met the USP requirements for weight variation of all formulae was less than 2% (USP 31). In all the formulations, the hardness test indicated good mechanical strength, whereas friability was less than 1%, which indicated that the tablets had a good mechanical resistance. The weight of all the formulations were ranged between 38.7 and 44.9 newton. Hardness of tablet is not a perfect parameter to check the mechanical strength. In this study, the percent friability for all the formulations was below 1%, indicating that the friability was within the compendia limit (USP 31). Wetting time of all the formulations ranged from 39 to 70 seconds.

In vitro deaggregation study

The most important parameter that needs to be optimized in the development of MMTs is the disintegration time. In the present study, all the tablet formulations disintegrated in a varied range of 19 to 60 seconds [Table 2]. In the USP disintegration test for MMT, the disintegration apparatus for oral tablets was used without the plastic covering disks, and 2 minutes was specified as the acceptable time limit for disintegration of the tablet, fulfilling the official requirements (<2 minutes) for MMTs (USP 31). The rapid and desired disintegration of tablets was due to the presence and good proportion of CCS, avicel PH 101, and pearlitol SD 200 which has been explained in the discussion.

In vitro dissolution studies

Figure 1 and Table 3 show the dissolution profile of carvedilol from the formulations. As shown, five minutes after starting the experiment, more than 85% of the drug was dissolved in the medium. According to the literature, the amount of drug dissolved from MMTs must exceed 80% in 15 minutes. Therefore, the resulting dissolution profile met the above-mentioned requirement. The fast dissolution of the drug from the formulations has been explained in the Discussion section.

Table 2: Physiochemical evaluation of experimental melt-in-mouth formulations (F1-F10)

Formulation code	Average weight of tablet (mg) ± SD	Thickness	Crushing strength (n)	Friability (%)	Wetting time (seconds)	Deaggregation time (seconds)	% drug content
F1	78.73±1.215	2.04±0.011	44.2±2.5	0.66±0.02	70±3	60±2	98.60±0.02
F2	79.95±0.162	2.03±0.01	41±1.8	0.51±0.01	61±2	33±1	97.40±0.05
F3	79.99±1.011	2.03±0.016	44.8±2.7	0.40±0.04	48±2	48±3	99.34±0.02
F4	80.01±0.458	2.02±0.012	39.6±2.1	0.51±0.01	49±2	55±2	100.30±0.09
F5	80.03±1.030	2.305±0.011	38.7±3.2	0.52±0.06	39±1	19±1	99.65±0.05
F6	79.89±1.15	2.08±0.010	40.9±1.9	0.41±0.01	45±1	24±2	101.40±0.04
F7	80.04±1.024	2.06±0.015	42.2±1.7	0.54±0.03	39±1	28±1	99.35±0.03
F8	79.89±0.56	2.03±0.018	43.1±2.8	0.68±0.03	36±2	23±4	97.80±0.03
F9	80.08±0.828	2.04±0.014	41.6±1.6	0.67±0.07	43±2	27±2	98.50±0.01
F10	80.01±1.308	2.06±0.017	40.2±2.8	0.60±0.03	46±2	37±4	96.90±0.01

SD: Standard deviation

Table 3: Dissolution profile (%) of melt-in-mouth tablet formulations (*n*=6)

Formulation code	Dissolution time (min)					
	2	5	10	15	20	25
F1	77.43±5.35	89.12±2.11	94.12±2.01	96.33±1.19	97.88±2.14	97.25±2.36
F2	63.23±5.21	85±2.89	88.23±2.01	93.11±1.01	93.26±2.41	94.24±2.45
F3	70.48±3.45	88.66±3.02	92.6±2.11	94.35±2.18	96.12±2.52	97.12±1.78
F4	71.25±4.21	86.45±3.11	91.41±4.12	92.45±2.56	93.81±2.96	96.01±3.58
F5	67.21±5.96	85.36±4.6	86.96±5.12	92.91±2.48	93.18±3.12	95.99±3.66
F6	73.12±3.88	89.64±4.51	91.56±5.88	95.12±3.03	96.88±1.99	97.89±5.12
F7	80.26±4.26	89.32±6.01	93.66±4.65	94.65±4.01	97.88±3.57	98.23±4.78
F8	65.8±5.12	86.99±5.88	93.82±3.41	95.21±4.36	96.51±3.78	97.35±4.36
F9	63.85±4.39	88.88±3.77	94.89±2.22	96.33±3.25	98.12±2.69	99.01±5.84
F10	56.59±3.88	85±2.86	89.24±3.03	91.14±2.29	91.59±2.49	92.42±5.99

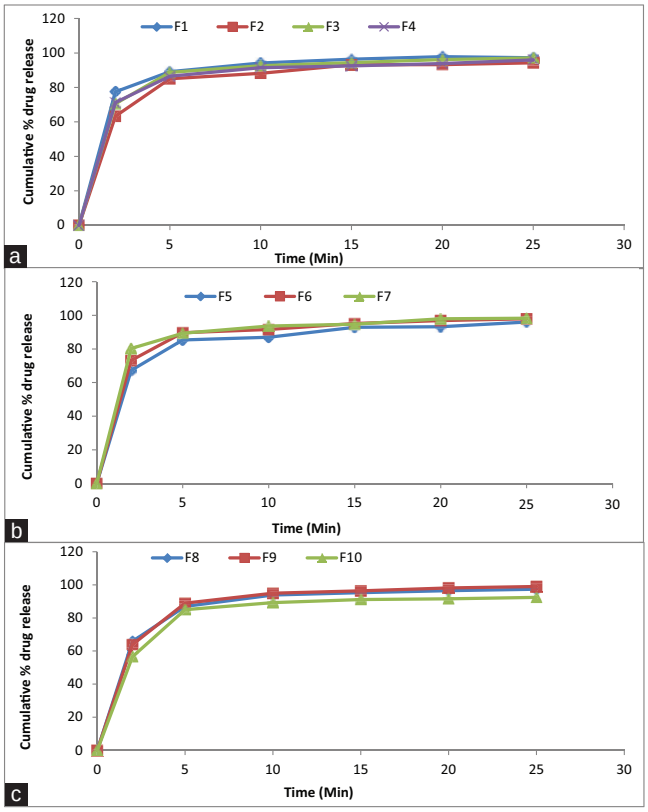

Figure 1: Dissolution profiles of melt-in-mouth formulations (F1-F10)

In vitro permeation studies

Permeation of drug from the formulations at the end of four hours was between 9.7 and 20.22% [Figure 2]. The low and slow release of drug can be attributed to small volume (2 mL) of the donor compartment which makes the tablets swell. Swollen particles have porosity, and release of drug occurs by diffusion through the openings created by the porosity of the matrix as described by Higuchi's square root equation. A higher swelling index ratio of Na-CMC may cause the diffusion pathway of the drug in the swollen matrix to extend and may decrease release of the drug.

Stability study

Accelerated stability studies were carried out at 30 ± 2°C, 65 ± 5°RH and 40 ± 2°C, 75 ± 5°RH for three months. All the physiochemical parameters were evaluated. There was no significant change in all physical parameters. Formulation F4,

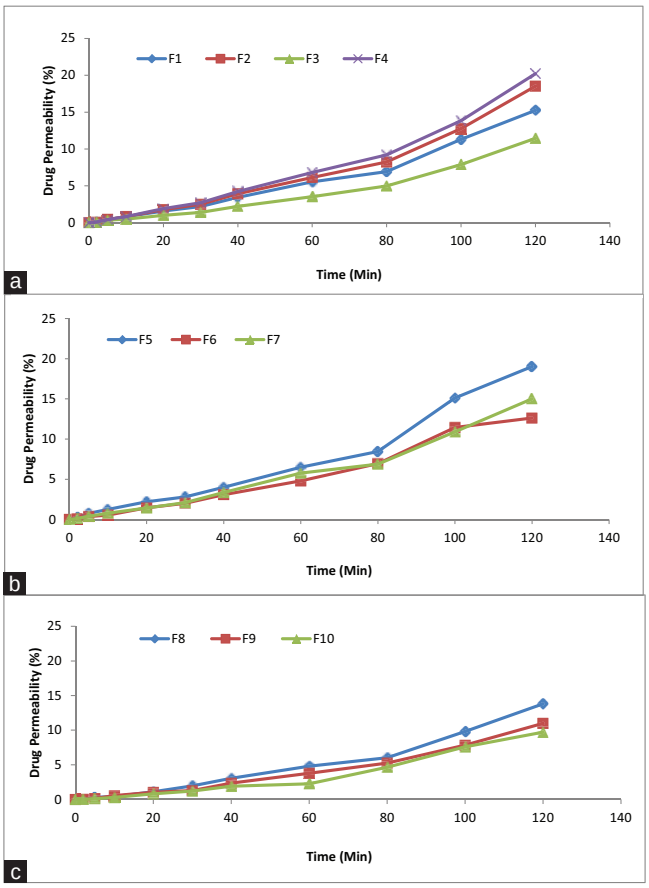

Figure 2: Permeation profiles of melt-in-mouth formulations (F1-F10)

F7, and F10 were subjected to dissolution testing and their drug release profiles were found to be comparable; so, they were shortlisted for further stability studies.

DISCUSSION

In vitro deaggregation study

Avicel has a good capacity to absorb. Tablets consisting of avicel disintegrate rapidly due to the rapid passage of water into the tablets resulting in the instantaneous rupture of the hydrogen bonds. The ratio of avicel in the tablet formulations was kept almost constant for all the formulations. Avicel accelerates water penetration into the tablets and enables easy swelling

of CCS; this reveals the superdisintegrant property of CCS. The ratio of CCS in MMTs is very important because it was reported that disintegration time increased with increase in the level of CCS in the tablets. It was shown that the increase in the level of CCS had a negative effect on the disintegration of the tablets. Higher concentrations of CCS lead to the formation of a viscous gel layer by CCS which might form a thick barrier to the further penetration of the disintegration medium and hinder the disintegration or leakage of tablet contents. Thus, disintegration is retarded to some extent with tablets containing CCS. So, it can be concluded that the use of CCS (cross carmilose sodium) in MMT formulations at a ratio of 2 % gives the desired disintegration time.[20]

On the other hand, pearlitol SD 200 has good water solubility, and this may leave pores on the tablet matrix after rapid dissolution of it. These pores can accelerate the capillary action that maybe responsible for penetration of the surrounding fluid in the tablet matrix and rapid disintegration thereafter.[21] The effect of different polymers on disintegration of tablets was optimized. Increasing the HPMC content in MMT formulations from 1.5, 3, and 3.5% ratios increased the disintegration time ($P > 0.05$). It was shown that increasing the concentration of HPMC caused an increase in the disintegration time of HPMC tablets. When HPMC tablets were exposed to water, HPMC absorbed water rapidly and formed a gelatinous layer on the tablet surface. This resulted in a poorly disintegrated tablet, and erosion became the main pathway for the size reduction of the tablet. When the concentration of the HPMC was less than 10%, the gel was not formed and the tablet could disintegrate easily.

Disintegration time increased with increase in the level of polymers in the tablets of chitosan and Na-CMC. This increase is significant in the formulations prepared with Na-CMC. This indicates that increase in the level of polymer had a negative effect on the disintegration of the tablets. From this result it was expected that at higher polymer ratios, formation of a viscous gel layer by polymers might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration of leakage of tablet contents.

In vitro dissolution study

In particular, pearlitol with a higher solubility might also facilitate the dissolution of solid dosage forms.[22] When dissolution was performed, within two minutes, chitosan-containing formulations gave the maximum release of drug [23]. This can be attributed to the fact that chitosan generously engulfs water when in contact with an aqueous medium and bursts due to the pressure exerted by the capillary action, thereby imparting instantaneous disintegration of the dosage form and resulting in the formation of a uniform dispersion in the surrounding medium which behaves like a true suspension formed inside the body leading to rapid dissolution of the drug. On the other hand, there were no significant findings between polymer content and dissolution rate of drug for the formulations containing HPMC and chitosan.[24] The tablet prepared with Na-CMC alone showed a correlation that increasing the polymer content of the formulation decreased the dissolution rate of the drug. This can be explained by the fact that a high ratio of polymer content in the formulation increases the diffusional pathway and decreases the water uptake and erosion of the tablets so as to decrease the dissolution of the drug. After evaluation of the tablets, it was found that polymer ratios (0.5–5%) enable preparation of MMTs without changing the basic characteristics of the tablet, especially the disintegration and dissolution profiles.[25]

CONCLUSION

All the prepared tablets met the compendia limits in terms of physiochemical parameters and disintegration and dissolution studies. HPMC, chitosan, and Na-CMC as mucoadhesive polymers at a ratio of 0.5-5% can be used in MMT formulations to provide the necessary time for carvedilol to be absorbed and protect it from the flushing action of saliva. When orally administered, carvedilol is well absorbed and becomes more bioavailable. As a result, MMT administration of carvedilol appears to be a promising alternative to traditional routes of drug administration.

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