Journal of Drug Delivery Science and Technology 47 (2018) 151–158

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Buccoadhesive gel of carvedilol nanoparticles for enhanced dissolution and bioavailability

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1. Introduction

Carvedilol is a member of α_1/β-adrenergic blockers, which has many pharmacological effects. It is used in the management of hypertension, cardiac arrhythmias and angina pectoris and as an adjunct to standard therapy in symptomatic heart failure. It is also used to reduce mortality in patients with left ventricular dysfunction after myocardial infarction. At higher doses, calcium-channel blocking activity may occur [1]. Although carvedilol has all these properties, it has poor bioavailability (25–35%) due to its poor water solubility and first pass effect [2]. Many approaches were studied to avoid the oral route and hence increase drug bioavailability through bypassing the first pass effect such as buccal [3], nasal [4] and transdermal [5] dosage forms. Buccal dosage forms of carvedilol were developed such as films, patches and tablets. Venkatalakshmi R et al. [6] developed carvedilol erodible mucoadhesive buccal film using HPMC E15 polymer. Anuj K et al. [7] formulated carvedilol buccoadhesive patches using HPMC K15 and carbopol 940 which exhibited drug release in the range of 77.05–97.2% in 8 h. Aijaz AS et al. [8] used HPMC K4M in preparation of carvedilol controlled buccal tablet formulation.

From the other side, to improve carvedilol poor water solubility, several trials had reported the improvement in dissolution properties of carvedilol by complexation with cyclodextrin [9], solid dispersion [10,11], nanoparticles [12], preparation of solid dispersions with porous silica [13] and preparing liquid–solid compacts [14]. Nanoparticles are one of the approaches which could increase the dissolution rate of carvedilol by physical modifications which increase the surface area, solubility and wettability of the drug particles [15,16].

Ionotropic gelation technique is one of the methods used for nanoparticles preparation which depends on precipitation of sodium alginate with calcium chloride and entrapment of drug inside these precipitated particles. Sodium alginate is an anionic polysaccharide consists of mannuronic and guluronic acid units linked with glycosidic bonds. Gelation is induced by cross-linking of the guluronic acid units with calcium chloride [17,18]. It had been used to prepare alginate beads and large alginate microspheres [19], as it was not useful for the preparation of small alginate nanoparticles [20]. Addition of a complexing agent such as poly-L-lysine [21] and Eudragit [22] permitted the preparation of stable alginate nanoparticles; the addition of such complexing agent allowed strengthening of the system to get small and well-defined particles [21].

The objective of this study included preparation of alginate nanoparticles of carvedilol using Eudragit® RS100 as a complexing agent, selection of optimized nanoparticles formula after *in vitro* evaluation and preparation of buccoadhesive gel using two mucoadhesive polymers and finally *in vivo* evaluation of the prepared gel formulae on rabbit models after *in vitro* and *ex vivo* evaluation.

2. Materials and methods

2.1. Materials

Carvedilol was supplied from (Sigma, Egypt) as a gift sample, sodium alginate was from (ACRŌS ORGANICS, USA), Eudragit® RS100 was kindly supplied from (Heinrich's commercial agency, Egypt), sodium carboxymethyl cellulose from (El-Nasr pharmaceutical chemicals company, Cairo, Egypt), hydroxypropyl methylcellulose K4M was kindly supplied from (GNP, Egypt), cremophor EL (Sigma-Aldrich, Germany), other surfactants (tween 80, labrasol and cetrimide) and calcium chloride were from (Merck, India). Acetonitrile and methanol were purchased from (Fisher scientific, UK). All other reagents used were of analytical grade.

2.2. Methods

2.2.1. Drug-excipient compatibility study

2.2.1.1. Differential scanning calorimetry studies. The physical compatibilities of carvedilol with polymers were studied using the differential scanning calorimetry analysis (DSC-60, Shimadzu, Japan). Carvedilol and physical mixtures samples in a ratio of 1: 1 were sealed in the standard aluminum pan separately and scanned between 40 °C and 430 °C under nitrogen atmosphere of flow rate 100 mL/min with a heating rate of 20 °C/min.

2.2.1.2. Fourier transform infra-red spectroscopy analysis. Chemical compatibilities of carvedilol with polymers used in the preparation

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https://doi.org/10.1016/j.jddst.2018.07.009
Received 8 December 2017; Received in revised form 30 June 2018; Accepted 10 July 2018
1773-2247/

were studied using Fourier transform infra-red spectroscopy analysis in a ratio of 1: 1. Samples were mixed with sufficient amount of KBr, pressed into a disk and scanned from 4000 to 500 cm^{-1} using FTIR spectrophotometer (Shimadzu, Japan).

2.2.2. Preparation of carvedilol nanoparticles

Factorial design was constructed using a statistical software program (MINITAB, version 17). Twelve carvedilol nanoparticles formulae were prepared based on $3^1 \times 4^1$ factorial design. Carvedilol: sodium alginate polymer ratio was used as the X_1 variable at 3 levels and surfactant type was used as the X_2 variable at 4 levels as shown in Table 1. Other factors (calcium chloride and Eudragit® RS100 concentrations) were kept constant.

After method optimization regarding surfactant type, calcium chloride concentration, time and speed of homogenization [22], a volume of 40 mL sodium alginate aqueous solution with a constant concentration (Sys.Conc.= 0.1% w/v) along the study was prepared to which the surfactant either tween 80, cremophor EL, labrasol or cetrimide (Sys.Conc.= 0.05% w/v) was added followed by the addition of 5 mL methanolic carvedilol solution. A volume of 2.5 mL calcium chloride aqueous solution (Sys.Conc.= 0.9 mM) was added dropwise. After 10 min homogenization (Stuart homogenizer SHM 1 provided with 7 mm probe, USA), a volume of 2.5 mL Eudragit® RS100 solution in 96% v/v ethanol in water (Sys.Conc.= 0.05% w/v) was added dropwise and the system was stirred for 30 min at 5000 rpm. The prepared nanoparticles suspension final volume was made 50 mL using distilled water. Each formula was made in triplicate.

Entrapment efficiency, dissolution efficiency (%$DE_{(6h)}$), median dissolution time (MDT) and particle size were selected as the dependent variables and the study of the effect of X_1 and X_2 on them was done using one way analysis of variance test. Post hoc test with CI = 95% was then conducted when significant differences (P value is < 0.05) present. One formula was selected for gel preparation.

2.2.3. Evaluation of the prepared carvedilol nanoparticles

2.2.3.1. Particle size. Particle size was determined using particle size analyzer (Mastersizer, 2000, Hydro, 2000MU, Malvern instruments, UK). Sample measurement was in the range of 0.02–2000 μm [23] with an obscuration value of 10%.

2.2.3.2. Entrapment efficiency. The entrapped amount of carvedilol was determined in the supernatant after separation of nanoparticles from 1 mL nanoparticles suspension using cooling centrifuge at 15000 rpm, 4 °C (Beckman, Fullerton, Canada) for 30 min [24]. It was estimated by using the high performance liquid chromatography stability indicating assay method developed by Mohammad R et al. [25] with slight modifications. Acetonitrile: 0.02 M potassium phosphate buffer adjusted to (pH 3.5) with phosphoric acid (55:45) v/v was used as the mobile phase. Hypersil BDS C18 (250*4.6 mm, 5 μm, USA) analytical column was used as the stationary phase. A volume of 20 μL was injected into high performance liquid chromatography system (HPLC, AGILENT 1260 infinity, quat pump VL, UV detector, chemstation software, Germany) and the chromatographic separation was achieved at a flow rate of 1 mL/min, 242 nm and ambient temperature. Amount of carvedilol in the sample was determined and the entrapment efficiency was determined by using the following formula: % Entrapment efficiency = (Mass of carvedilol in nanoparticles/Mass of carvedilol used in formulation) × 100 [26].

2.2.3.3. In vitro release. The study was performed using 10 mg carvedilol equivalent nanoparticles suspension, which added to 500 mL 0.05 M potassium phosphate buffer (pH 6.8) [27,28] using dissolution apparatus II (Agilent technologies 708-DS, USA) at 50 rpm and 37 ± 0.5 °C. Samples of 2 mL were removed at specified time intervals up to 6 h and centrifuged at 15000 rpm, 4 °C for 5 min. The precipitate was resuspended in 2 mL fresh phosphate buffer and returned to the dissolution vessel [29].

The percentage of released carvedilol was calculated after HPLC measurement as mentioned before, using a calibration curve in 0.05 M

Table 1
Composition and evaluation parameters of the prepared carvedilol nanoparticles according to $3^1 \times 4^1$ factorial design (data represented as mean ± SD).

	Variables		Response values			
	X_1	X_2	MDT[a] (min) ± SD	DE $_{(6h)}$[b] (%) ± SD	Entrapment efficiency (%) ± SD	Particle size (nm) ± SD
F1	1	−2	7.86 ± 0.43	69.72 ± 1.38	73.3 ± 1.17	169.7 ± 1.04
F2	1	−1	8.2 ± 0.14	67.42 ± 1.72	86.33 ± 0.25	170 ± 0
F3	1	1	9.45 ± 1.4	60.25 ± 1.99	73.51 ± 2.05	156 ± 0
F4	1	2	7.22 ± 0.64	58.67 ± 1.08	73.74 ± 0.55	170 ± 1.57
F5	0	−2	7.1 ± 1.34	58 ± 0.97	78.85 ± 0.27	170.7 ± 0.58
F6	0	−1	6.93 ± 0.17	64.15 ± 1.04	80.15 ± 0.72	175.7 ± 1.53
F7	0	1	10.4 ± 0.2	58.52 ± 0.92	90.33 ± 0.46	224.7 ± 1.52
F8	0	2	5.36 ± 0.87	73.84 ± 1.17	95.34 ± 1.72	189.7 ± 1.03
F9	−1	−2	5.28 ± 0.26	66.55 ± 1.68	91.06 ± 0.69	160 ± 0.58
F10	−1	−1	5.8 ± 0.34	83.55 ± 1.29	99.2 ± 0.52	150.3 ± 1.53
F11	−1	1	4.7 ± 0.22	94.1 ± 1.76	91.35 ± 1.69	161.3 ± 1.52
F12	−1	2	7 ± 1.6	87.06 ± 1.84	98.77 ± 0.00	163 ± 2

Coded values		Actual values	
		X_1	X_2
Very low	−2	–	Tween 80
Low	−1	2:1	Cremophor EL
Intermediate	0	1:1	–
High	1	1:2	Labrasol
Very high	2	–	Cetrimide

% $DE_{(6h)}$ for carvedilol suspension was 27.4 ± 1.34%, while MDT was 17.1 ± 1.95 min.

[a] $MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$ (n is the number of dissolution sample times, j is the sample number, $\hat{t}_j$ is the time at midpoint between t_j and t_{j-1} and ΔM_j is the additional amount of drug released between t_j and t_{j-1}) [33].

[b] $\%DE = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\%$ (y is the percentage of drug released at time t) [32].