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Effect of hydrophilic substances on liberation of quinidine from starch – methylcellulose spheres

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Abstract

The spheres were prepared by the desolvation technique combined with gravitational sedimentation of droplets of methylcellulose gel suspensions with the addition of 25 % quinidine adsorbate on the potato starch and 5 % hydrophilic agents such as Span 80, Tween 60, glyceryl monostearate or PEG 2000 instilled into a desolvation liquid (saturated sodium acetate : paraffin liquid : heptane 1:1:1, v/v/v) through a standardized capillary.

As follows from the physicochemical studies the sphericity (Sp) changed within the range 1.020 – 1.314, the porosity (P) was 19.1 – 66.5 % and the loading efficiency was 35.10 – 67.07 %. The release studies show that the dissolution efficiency after 60 min (DE_{60}) in acidic medium was 78.6 % for quinidine and 52.6 – 63.4 % for the spheres; in phosphate buffer pH 6.8 DE_{60} was 32.4 % for quinidine, but ranged within 16.3 – 26.0 % for the spheres. The release of the drug from the spheres was fast and it was slightly difference (the loaded drug was released within 60 min) in acidic medium, while differentation of release in the phosphate buffer made it possible to evaluate the effect of hydrophilic additives on the dissolution rate.

The general process of release can be described by the modified Higuchi equation $M_t^{\cdot} = K_0 \cdot \left(\sqrt{t} - \sqrt{T_D}\right)$, which facilitates the analysis of the theoretical amount of

the released substance (M_t^*) depending on the zero-order dissolution rate constant (K_0) and the dissolution lag time (T_D). Accordingly, spheres with sustained release can be most effectively produced by addition of PEG 2000. These spheres are characterized by Sp = 1.035, P = 60.2 % and a loading efficiency of quinidine 67.07 %. The release in acidic medium proceeds with K_0 = 3.857 mg·min$^{-0.5}$ and T_D = 6.21 min, in phosphate buffer K_0 was 1.293 mg·min$^{-0.5}$ and T_D = 7.14 min. These parameters were of less importance for the other formulations. The modified Higuchi equation gives information about the parameters of drug released.

Keywords

Quinidine, spheres, loading, release.

Introduction

Special type granules (spheres) are prepared by different spheronization methods (1) such as polymer or monomer emulsification techniques (2,3) with the organic or aqueous continuous phase, solvent evaporation from emulsion (4), multiphase emulsification (5), molten dispersion (6), spray drying (7), extrusion – spheronization (8). Emulsification techniques comprise formation of an emulsion from a dispersed phase which is a solution of a monomer or a polymer in a volatile solvent including a dispersed or suspended medicinal substance made up of water or oil with the addition of emulsifier; evaporation of the solvent, and finally hardening of the particles. The multistage character of the process requires the use of suitable quality homogenizers and apparatus intercepting volatile vapours of the solvent or utilizing post – reaction mixtures. A number of intermediate stages is significantly reduced using the drug – carrier dispersion technique, the spray drying of aqueous or organic solvent suspensions method and the extrusion – spheronization technique. These techniques

require expensive technical equipment to produce particles of different diameters which are not always spherical and uniform in size.

For higher efficiency, the following auxiliary substances are used for production of spheres: carriers such as cellulose and its derivatives (9,10), proteins (11), starch (12), synthetic polymers (13), solvents such as methylene chloride (14), chloroform (15), acetone (16), ethanol (17), water (18), corn oil (19), nonionic emulsifiers – cetyl alcohol (20), polysorbate 65 (21), solubilizers such as PEG 1500 and PEG 4000 (1) and plasticizers (22).

Spheres are delivery systems for drugs from different therapeutic groups such as gentamicin sulphate (11), methotrexate (23), acyclovir (24), indomethacin (25), acetylsalicylic acid (26), sodium cromoglycate (27), progesterone (28), insulin (29), valproic acid (30), propranolol hydrochloride (31), tetanus vaccine (32). The rationale for incorporation of these drugs into the spheres was to decrease side effects (e. g. to reduce local irritation of anti – inflammatory drugs), to prolong therapeutic activity, to increase bioavailability or to sustain the release of the active ingredient.

Spheres are characterized by physical analysis of size (33), sphericity (34), true and relative density (35), porosity (36) and efficiency of drug loading (1).

The release of active agents is tested according to pharmacopoeal methods recommended for tablets (BP 93, USP XXII, Eur. Ph. 3rd Edition 1996).

Literature lacks sufficient data on preparing quinidine spheres by the technique of desolvation of suspensions of starch – methylcellulose sorbats into a desolvation liquid. Therefore, the aim of this study was to prepare the spheres by desolvation of concentrated suspensions with different composition and to determine the effect of hydrophilic substances on the efficiency of loading, and on the kinetics of quinidine release in artificial gastric or intestinal fluids.

Results and Discussion

The compositions of spheres are shown in Table 1.

Table 1. The formulations of quinidine spheres

Components (mg)	I - 0	I - 1	I - 2	I - 3	I - 4
(Q + AS)	4000	4000	4000	4000	4000
MC	750	750	750	750	750
Span 80	-	250	-	-	-
Tween 60	-	-	250	-	-
MSG	-	-	-	250	-
PEG 2000	-	-	-	-	250
Water contents for gel	13	12	13	13	13
Water contents for dilutions	-	0.5	1	1	-

In accordance with the formulations given in Table 1, quinidine spheres were prepared using the desolvation and gravitation technique consisting in instilling sticky suspensions into the desolvation medium. The desolvation medium consists of three liquids: the upper layer was heptane, the medium one was paraffin oil, and the lower was a saturated solution of sodium acetate. Droplets falling through the hydrophobic layers were rounded, and next their surface areas became hydrophobic. Then they slowly shifted into the saturated solution of sodium acetate, where the droplets underwent desolvation and were rounded and hardened after 0.5 h. Macroparticles were dried at room temperature and stored in a desiccator over anhydrous calcium chloride. The metod proposed for sphere production is simple, economic and does not require complicated technical equipment. Moreover, homogeneous spherical particles can be obtained using capillaries of standardized outlet. The desolvation liquid can be used many times after the previous saturation of sodium acetate of the liquid. For the production of spheres evaporation, utilization of toxic solvent vapours, and other chemicals harmful for the environment is not necessary.

The obtained spheres were evaluated by their physical characteristics.

Table 2. Physical characteristics of quinidine spheres

Spheres	Size			Weight		V	ρ_r	ρ_t	P
	L(mm)	SD (%)	Sp	m (mg)	SD (%)	(mm^3)	(g/cm^3)	(g/cm^3)	(%)
I-0	2.825	5.2	1.314	5.109	4.0	8.06	0.634	1.372	53.8
I-1	2.135	7.6	1.076	4.460	3.4	4.57	0.976	1.275	23.5
I-2	2.137	7.3	1.044	4.755	3.6	4.78	0.995	1.230	19.1
I-3	3.000	2.2	1.020	5.440	2.8	13.71	0.397	1.184	66.5
I-4	2.955	3.2	1.035	6.660	4.1	12.83	0.519	1.305	60.2

The data in Table 2 show that the long axis (L) changed within the range 2.135 – 3.000 mm. The sphericity (Sp) was calculated using the equation (34): Sp = (L/l), where l is a short axis and Sp changed from 1.020 to 1.314. Spheres with hydrophilic substances had a round shape, but those only with methylcellulose were oval. The average mass of spheres ranged between 4.460 mg and 6.660 mg within the range ± 10 %. Preparations obtained according to the compositions (I-3) are characterized by low relative density (ρ_r) 0.397 g/cm^3, the (I-4, I-0) groups have slightly higher density 0.519 – 0.634 g/cm^3, and a density close to the value of 1 is noted in the spheres (I-1, I-2) 0.976 – 0.995 g/cm^3.

The porosity of spheres (P) was calculated according to the equation (36): $P = [(1-\rho_r/\rho_t)]\cdot 100\%$. The relative density ($\rho_r$) of spheres was calculated as the ratio between the beads mass and the beads geometrical volume (V), where $V = 1/6\cdot\Pi\cdot[(L+l)/2]^3$ (37). The porosity increases from 19.1 % to 66.5 % proportionally to the decrease in relative density. The addition of MSG (I-3) and PEG 2000 (I-4) causes a smaller increase in porosity of spheres 12.7 – 6.4 %; Span 80 (I-1) and Tween 60 (I-2) significantly decrease the porosity of those spheres (30.3 – 34.7 %) which may depend to some extent on the hydrophilic character of these components.

Table 3. Loading efficiency of quinidine spheres (n = 6)

Spheres	Quinidine contents (mg) in 200 mg dry mass			Loading
	added	recovered	SD (%)	efficiency (%)
I-0	42.10	19.81	4.8	47.06
I-1	40.00	19.93	4.1	49.82
I-2	40.00	23.81	3.2	59.52
I-3	40.00	14.04	7.1	35.10
I-4	40.00	26.83	4.5	67.07

The loading efficiency of the active substance (Table 3) changes from 35.10 % to 67.07 %. The spheres with MSG (I-3) were characterized by the lowest efficiency 35.10 %. The spheres with MC or Span 80 (I-0, I-1) exhibited a loading efficiency about 50 % (47.06 – 49.82 %), while those with Tween 60 (I-2) and PEG 2000 (I-4) had the highest efficiency 59.52 – 67.07 %.

The macrospheres (I-2) and (I-4) are most favourable.

The release of quinidine was significantly affected by pH of the dissolution media.

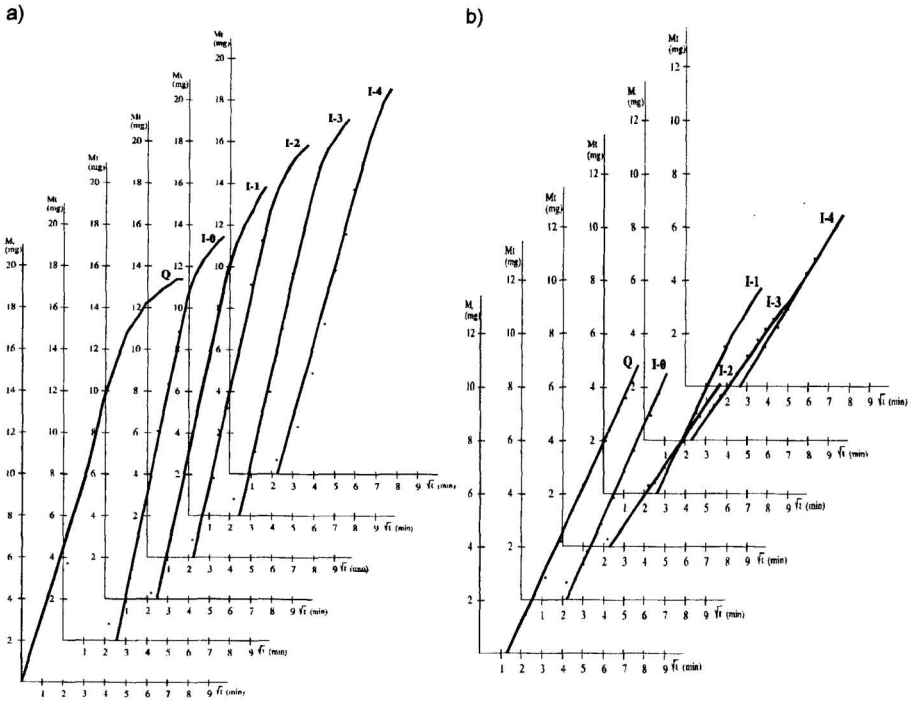

Figure 1. Effect of hydrophilic agents on liberation of quinidine from spheres into a) HCl (0.1 mol/l), b) phosphate buffer pH 6.8

Figure 1 shows that 92.8 - 99.9 % of the substance was released from macrospheres (M_0 = 20 mg) in acidic medium due to formation of readily soluble salts – quinidine hydrogen chloride. However, the amount of the released substance (M_t) of the function $\sqrt{t}$ has a rectilinear character until 85 – 87.5 % are released from all spheres. In phosphate buffer only 30 – 49 % quinidine is released from the spheres, 54 % (Q) which runs according to function.

The F values indicate that the quinidine release was in accordance with the Higuchi equation (1,6):

$$M_t^* = K_0 \cdot \left(\sqrt{t} - \sqrt{T_D}\right)$$

$$F = (M_t^* / M_t) \cdot 100,$$

$$K_0 = (M_2 - M_1) / (\sqrt{t_2} - \sqrt{t_1}),$$

$$T_D = [(K_0 \cdot \sqrt{t} - M_t) / K_0]^2,$$

where M_t^* is the theoretical amount of the released substance, M_t is the released amount of the substance after 60 min, T_D is the dissolution lag time, K_0 is zero-order dissolution rate constant, M_1 is the total amount of the released substance after the time t_1, M_2 is the total amount of the released substance after the time t_2 and M_0 is the initial dose of quinidine.

The parameters of release are M_t, R_M, and DE_{60} and they can be calculated according to equations:

$$R_M = (M_t / M_0) \cdot 100\%,$$

$$DE_{60} = (AUDC/M_0 \cdot 60) \cdot 100\%,$$

$$AUDC = \int_0^{60} M_t \cdot dt,$$

where R_M is the recovery calculated from the quotient mass, DE_{60} is the dissolution efficiency after 60 min and AUDC is the area under the graphs of quinidine release. These values are presented in Tables 4 and 5.

Table 4. Liberation kinetics of quinidine from spheres in 0.1 M HCl (n = 6)

Spheres	t (min)	M_0 (mg)	M_t (mg)	SD (%)	R_M (%)	K_0 (mg ·min$^{-0.5}$)	T_D (min)	$AUDC_0$ (mg ·min)	DE_{60} (%)	F (%)
Q*	60	20	19.98	4.17	99.9	3.365	0	943.20	78.6	99.6
I-0	60	20	19.40	1.63	97.0	5.085	6.58	739.61	61.6	98.6
I-1	60	20	19.76	2.62	98.8	4.486	5.67	722.12	60.2	98.2
I-2	60	20	19.85	1.83	99.2	4.593	5.06	760.45	63.4	94.3
I-3	60	20	19.04	1.47	95.2	4.513	6.10	704.33	58.7	100.5
I-4	60	20	18.57	4.71	92.8	3.857	6.21	630.69	52.6	95.1

Q* - quinidine in substance

Table 5. Liberation kinetics of quinidine from spheres in phosphate buffer pH 6.8 (n = 6)

Spheres	t (min)	M_0 (mg)	M_t (mg)	SD (%)	R_M (%)	K_0 (mg ·min$^{-0.5}$)	T_D (min)	$AUDC_0$ (mg ·min)	DE_{60} (%)	F (%)
Q*	60	20	10.80	1.05	54.0	1.622	1.26	388.67	32.4	99.4
I-0	60	20	9.71	1.79	48.5	1.702	4.73	311.49	26.0	97.6
I-1	60	20	6.08	3.40	30.4	1.091	5.15	195.22	16.3	98.2
I-2	60	20	8.03	2.54	40.1	1.645	6.79	257.49	21.5	98.5
I-3	60	20	5.90	3.17	29.5	1.162	5.40	199.66	16.6	100.3
I-4	60	20	6.37	2.70	31.8	1.293	7.14	201.72	16.8	96.2

The data in Table 4 and Figure 1a indicate that the auxiliary agents included in formulations I-1, I-2, and I-0 do not impede the release of quinidine to 0.1 M HCl; R_M is 98.8 %, 99.2 %, 97.0 %, and DE_{60} is 60.2 %, 63.4 %, 61.6 % with K_0 4.486 mg·min$^{-0.5}$, 4.593 mg·min$^{-0.5}$, 5.085 mg·min$^{-0.5}$, respectively. The release rate of the substance decreases successively with the spheres I-3, I-4 in which the values R_M are 95.2 %, 92.8 %, respectively. This is confirmed by the K_0 values of 4.513 mg·min$^{-0.5}$ and 3.857 mg·min$^{-0.5}$, and the DE_{60} 58.7 % and 52.6%.

The dissolution of quinidine – base in phosphate buffer pH 6.8 proceeded very slowly – R_M = 54 % within 60 min with DE_{60} = 32.4 % and K_0 = 1.622 mg·min$^{-0.5}$. The data in Table 5 and Figure 1 b show that the release of the substance from spheres

I-0, I-2 is similar to quinidine – base, but the addition of Span 80 (I-1), MSG (I-3), PEG 2000 (I-4) to the formulations slowed down the release process (R_M = 29.5 – 31.8 %, DE_{60} = 16.3 – 16.8 %, K_0 = 1.293 mg·min$^{-0.5}$ – 1.091 mg·min$^{-0.5}$).

In the facts the new desolvation technique of concentrated suspensions in a three-layer solvent mixture is suitable for preparation spheres with quinidine. Sphericity and loading efficiency of quinidine depend on a hydrophilizing agent being used. In acidic medium, the amount of the released substance from the spheres after 60 min was higher than in phosphate buffer. The introduction of the hydrophilic agents to the starch – methylcellulose spheres caused some changes in the quinidine release. The sustained release of quinidine spheres can be most effectively achieved based on the formula consisting of the quinidine adsorbate, methylcellulose, PEG 2000 at the ratio 16:3:1 (w/w/w). Liberation kinetics from all spheres can be described by the modified Higuchi equation, which characterizes the process by means of the analyses of the dissolution rate constants and the dissolution lag time.

Experimental

Materials

Quinidine (Q, Sigma), potato starch (AS, Pol.Ph.V), methylcellulose (MC, Fluka), sorbitan monooleate (Span 80, Aldrich), polyoxyethylene 20 sorbitan monostearate (Tween 60, Merck), glyceryl monostearate (MSG, Fluka), polyethylene glycol 2000 (PEG 2000, Fluka).

Preparation of quinidine adsorbate

30 g quinidine was dissolved in 500 ml ethanol in a 1000 ml cone flask. Next, 90 g potato starch, dried at 40^{0}C, was added to the flask and stirred for 1 h. The suspension was kept at room temperature for 24 h. After filtration through a Whattman membrane

filter, the adsorbate was dried at 40^{0}C and powdered. The initial and recovered amount of quinidine was equal to 1000 mg in 4000 mg of adsorbate (Q + AS).

Quinidine and its salts administered orally can cause irritation of the gastrointestinal tract with the symptoms of nausea, vomiting and diarrhoea. The quinidine adsorbate on potato starch used for production of spheres can reduce the irritation effect significantly, decrease the absorption of the drug from the initial part of the gastrointestinal tract, and prolong the release of the drug from the spheres.

Preparation of spheres

The quinidine adsorbate and the hydrophilic substances were ground and then suspended in methylcellulose gel. The suspension was stored at 4^{0}C for 24 h to improve rheological properties and after warming to room temperature, it was diluted with an appropriate amount of water and dropped from 9 – 10 cm height into the desolvation medium consisting of sodium acetate saturated solution, liquid paraffin, n – heptane (50 : 50 : 50, v/v/v) through a capillary tube of 0.9 mm in diameter. The spheres were kept in the desolvation liquid for about 30 min. Then they were filtered, washed with water, dried at room temperature, and stored in a desiccator over anhydrous calcium chloride.

Physical characteristics

The spheres size (mm diameter) and weight (mg) were determined by measuring the long (L) and short (l) axes of 100 sphere units and weighing 100 sphere units (stereoscopic microscope, type MSt 127: with a magnification x 21 Poland, analytical balance type Metter AT 201 Switzerland).

The true density (ρ_t) of spheres was measured by using a pycnometer with ethanol (760 g/l) as a dispersion liquid at room temperature.

Drug content

The assay procedure was similar to "Quinidine Sulfate Capsules" in USP XXII. Dried spheres were powdered and accurately weighed 200 mg powder was transferred into a 100 ml volumetric flask and hydrochloric acid solution (0.1 mol/l) was added. Then, the mixture was shaken for 0.5 h and left for 10 min. The mixture was filtered by the Whattman membrane filter of 0.45 μm pore size, discarding the first 20 ml of the filtrate. Next 5 ml of the filtrate was transferred to a 100 ml volumetric flask and hydrochloric acid solution (0.1 mol/l) was added to the volume. The absorbances of this solution were determined in a 1-cm cell at 250 nm, with a spectrophotometer (Spectromom 195, Hungary), using hydrochloric acid solution (0.1 mol/l) as a blank. The content of active ingredient (M) was calculated from $M = \left[A/a^{1\%}_{1cm}\right] \times 20000$ (mg) in which A is the absorbance of assayed solution, $a^{1\%}_{1cm} = 880$ is the specific absorbance.

Release study

The release study was carried out in a miniflow – cell apparatus (38) similar to the cell in Eur. Ph. 1996 at 37^{0}C in the two dissolution media – hydrochloric acid solution (0.1 mol/l) and phosphate buffer at pH 6.8 (Pol.Ph.V) – at a constant flow rate of about 2.0 ± 0.1 ml/min. The accurately weighed samples of spheres with the theoretical content equivalent to 20 mg of quinidine base were placed in the dissolution cell and 10 ml portions of eluate were collected. The content of released quinidine was assayed spectrophotometrically after appropriate dilution of the samples with HCl (0.1 mol/l). Each measurement was performed six times for each preparation.

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