AAPS PharmSciTech, Vol. 11, No. 1, March 2010 (© 2010)
DOI: 10.1208/s12249-009-9359-2

Research Article

Effect of Formulation Parameters on the Preparation of Superporous Hydrogel Self-Nanoemulsifying Drug Delivery System (SNEDDS) of Carvedilol

Enas Ahmed Mahmoud,[1,2] Ehab R. Bendas,[1] and Magdy I. Mohamed[1]

Received 5 May 2009; accepted 9 December 2009; published online 3 February 2010

Abstract. The purpose of this study was to formulate a superporous hydrogel (SPH) containing carvedilol self-nanoemulsifying drug delivery system. Effects of formulation parameters (amount of SPH and 0.1 N HCl used during drug loading) were studied in 3^2 factorial design. Response surface plots showed significant effect of the parameters on hydrogel swelling, carvedilol content, and carvedilol *in vitro* release. Regression equations were generated to calculate the desirable responses.

KEY WORDS: carvedilol; self-nanoemulsifying drug delivery system; superporous hydrogel.

INTRODUCTION

Hydrogels are known as three-dimensional, hydrophilic, polymeric networks capable of impeding large amounts of water or biological fluids (1). The high water content of the materials contributes to their biocompatibility and wide use in the medical and pharmaceutical areas (2–5).

The swelling properties of hydrogels are affected by their manufacturing process and the materials used during their preparation (6). Slow diffusion of water through the hydrogel structure produces slow-swelling process. Although slow swelling made hydrogels useful in controlled drug delivery, many applications required fast swelling. Fast swelling is usually done by making very small particles of dried hydrogels or preparing porous hydrogels (2,4,7). In this study, a superporous hydrogel (SPH) was synthesized using the gas blowing technique (8). It was then used as carrier for a liquid self-nanoemulsifying drug delivery system (SNEDDS) changing it into solid state. Impact of different parameters (amount of SPH and 0.1 N HCl used during drug loading) were studied using a factorial design. The response surface plots of the design were generated using Design-Expert® 7.0.0 software.

MATERIALS AND METHODS

Experimental Design

A two-factor, three-level, full-factorial design was used in this study to construct a quadratic model using polynomial analysis (Design-Expert® 7.0.0). Table I summarizes the dependent parameters and responses included in the study.

Materials

Polyoxyl hydrogenated castor oil (HCO-40) was purchased from CISME (Italy). Miglyol® 812 (medium chain triglycerides) was kindly provided by Sasol Company. Transcutol® HP was kindly provided by Gattefosse Company (France). Carvedilol was provided by Hetero Drugs Company (India). Hydrochloric acid, potassium dihydrogen phosphate, disodium hydrogen phosphate, absolute ethyl alcohol, and sodium bicarbonate were obtained from Adwic, El-Nasr Pharmaceutical Company (Egypt). Methocel® E15 LV (HPMC 15 cp) was kindly provided by Colorcon Company (UK). Acrylic acid (AA), acrylamide (AM), *N*,*N*'-methylenebisacrylamide (Bis), ammonium persulfate (APS), and *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) were provided from Sigma–Aldrich Chemical Company (USA). Pluronic® F127 (PF-127) was purchased from BASF Corporation, Chemical division (USA).

Synthesis of Superporous Hydrogel

According to Chen *et al.* (8), the following substances were added subsequently at ambient temperature to prepare poly(acrylamide-*co*-acrylic acid) superporous hydrogel (*P*(AM-*co*-AA) SPH): 1,000 μl AM 50%; 45 μl AA; 200 μl *N*,*N*'-methylenebisacrylamide (Bis) 2.5%; 460 μl water; 100 μl Pluronic® F127 (PF-127) 10%; 40 μl APS 20%; 40 μl TMEDA 20%; and 90 mg of sodium bicarbonate. The superporous hydrogel was dehydrated using absolute ethanol followed by drying in an oven at 50°C for 1 day and finally processed using a double-blade chopper.

[1] Faculty of Pharmacy, Cairo University, Cairo, Egypt.
[2] To whom correspondence should be addressed. (e-mail: enasamahmoud@gmail.com)

Table I. Different Combinations Used to Prepare *P*(AM-*co*-AA) SPH Containing SNEDDS-9 or 5% HPMC 15cp Using 3^2 Factorial Design

Run	Variable X_1: *P*(AM-*co*-AA) SPH (mg)	Variable X_2: 0.1 N HCl (*X*)
1	100 (−1)	20 (0)
2	200 (0)	10 (−1)
3	200 (0)	30 (+1)
4	100 (−1)	10 (−1)
5	200 (0)	20 (0)
6	300 (+1)	20 (0)
7	200 (0)	30 (+1)
8	300 (+1)	20 (0)
9	300 (+1)	30 (+1)
10	300 (+1)	10 (−1)
11	300 (+1)	10 (−1)
12	300 (+1)	30 (+1)
13	200 (0)	20 (0)
14	100 (−1)	30 (+1)
15	100 (−1)	20 (0)
16	200 (0)	10 (−1)
17	100 (−1)	30 (+1)
18	100 (−1)	10 (−1)

Values in brackets indicate coded levels of variables

Incorporation of SNEDDS into Superporous Hydrogel

One hundred milligrams of SNEDDS-9 or 5% HPMC 15cp (SNEDDS-9 is composed of 60% HCO-40, 10% Miglyol®, and 30% Transcutol®, medicated with 12.5% carvedilol, and finally, 5% HPMC 15cp was dispersed in it) were added to a beaker containing the predetermined amount of 0.1 N HCl and stirred to disperse the system.

Table II. Responses Obtained for the Studied Parameters from the Experimental Design

	Parameters		
Run	Y_1: Volume swelling ratio	Y_2: Carvedilol content (%)	Y_3: Release after 45 min (%)
1	2.75	87.69	42.99
2	5.16	108.36	88.66
3	2.83	82.32	65.67
4	4.83	103.32	88.16
5	3.33	78.96	56.49
6	3.50	82.32	54.91
7	2.66	99.96	67.65
8	3.66	87.36	58.45
9	2.33	63.00	56.10
10	6.33	102.48	86.52
11	6.00	99.96	85.77
12	3.00	66.36	58.65
13	3.33	82.32	53.55
14	2.33	99.96	64.72
15	3.00	94.33	39.19
16	5.16	106.68	88.95
17	2.83	99.96	70.61
18	4.83	103.32	90.05

Table III. Regression Equations for the Responses

$$Y_1 = 3.24 + 0.35X_1 - 1.36X_2 - 0.31X_1X_2 + 0.038\,X_1^2 + 0.76\,X_2^2$$
$$Y_2 = 87.01 - 7.26X_1 - 9.38X_2 - 8.30X_1X_2 - 2.26\,X_1^2 + 9.14\,X_2^2$$
$$Y_3 = 53.48 + 0.39X_1 - 12.06X_2 - 1.83X_1X_2 - 3.82\,X_1^2 + 25.03\,X_2^2$$

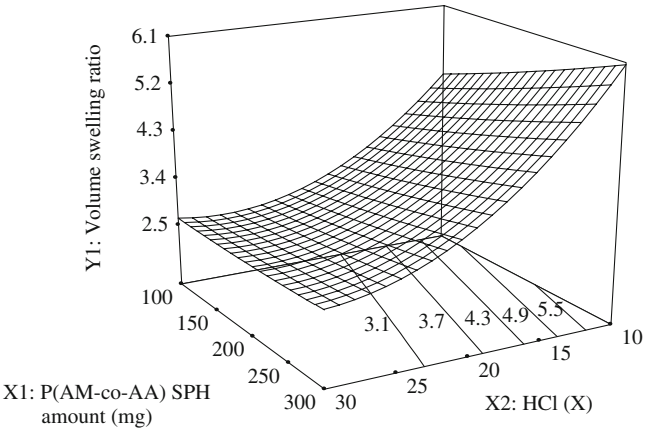

Fig. 1. Response surface plot showing the impact of formulation parameters on volume swelling ratio

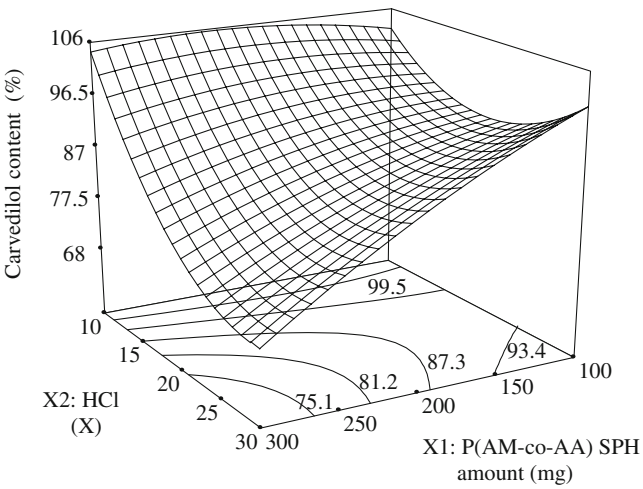

Fig. 2. Response surface plot showing the impact of formulation parameters on carvedilol content

Subsequently, the SPH was added and left for 1 h to ensure complete swelling. The hydrogel was dried then left on a filter paper for 24 h to remove any unabsorbed SNEDDS-9 or 5% HPMC 15cp. The amounts of the hydrogel and HCl (0.1 N) used in the preparation processes are presented in a factorial design as shown in Table I. The amount of 0.1 N HCl was used in three levels: 10, 20, and 30 times the amount of SPH in each level (in each run, the amount of 0.1 N HCl=10, 20, 30 times SPH amount in milligrams).

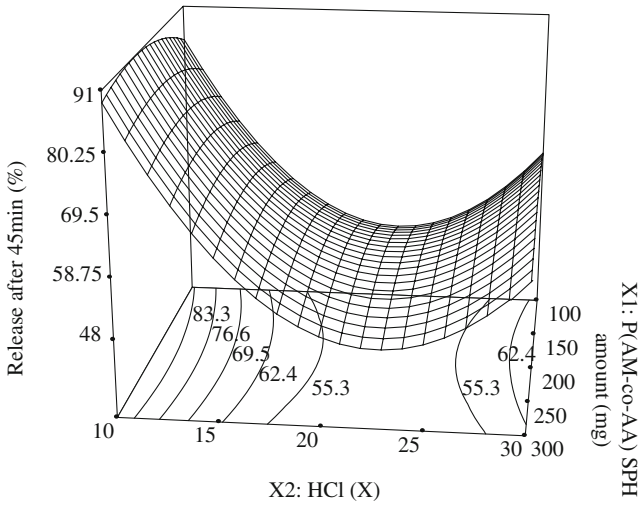

Fig. 3. Response surface plot showing the impact of formulation parameters on carvedilol release after 45 min

Evaluation of Superporous Hydrogels

Swelling Studies

Swelling studies of *P*(AM-*co*-AA) superporous hydrogels were carried out using volume swelling ratio method (9). Each of the SPH powders was placed in a 10-ml measure. Excess 0.1 N HCl at 37±0.5°C was added. The volume of the swollen SPH was measured after 45 min. This method avoided direct handling of the gel.

The volume swelling ratio (Q_v) is defined as: $Q_v = V_s/V_d$

Where V_s is the volume of swollen sample, and V_d is the volume of dried sample.

Estimation of Drug Loading

Each hydrogel was added to a container of 500 ml 0.1 N HCl and stirred using a paddle for 90 min at 37±0.5°C. Finally, the solution was filtered using a filter paper, and the absorbance of the solution was determined after making the appropriate dilution at λ_{max} 285 nm using 0.1 N HCl as a blank.

In Vitro Release Studies

The *in vitro* release of carvedilol from the prepared SPH was studied using USP dissolution apparatus, type II. The release studies were carried out at 37±0.5°C in 500 ml of 0.1 N HCl for 1 h. The paddles rotated at 50 rpm, and 5 ml aliquots were withdrawn from the release medium at predetermined time intervals and replaced with equal volumes of the release medium. The aliquots were filtered and assayed spectrophotometrically at 285 nm.

Morphological Analysis of SPH

Morphology of SPH porous structure was examined using a scanning electron microscope (SEM; Jeol JXA-840A, Japan).

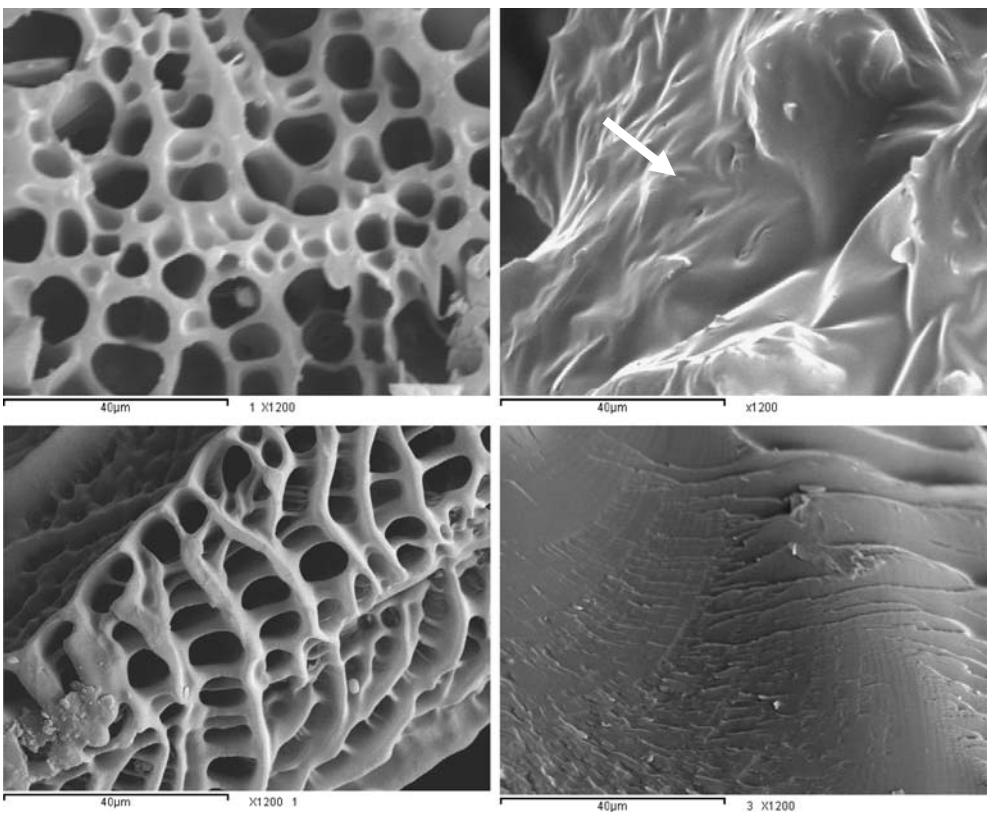

Fig. 4. Scanning electron microscope photomicrographs (×1,200) of: **a** SPH, **b** lyophilized SPH, **c** Carvedilol *P*(AM-*co*-AA) SPH, **d** lyophilized carvedilol *P*(AM-*co*-AA) SPH. The *arrow* points to an opening in the interconnected channels

Powders were fixed on a brass stub using double-sided adhesive tape, and then coating was made by electrical conductivity, in a vacuum, with a thin layer of gold (approximately 150 Å) for 30 s. The pictures were taken at an excitation voltage of 20 kV.

Particle Size Analysis

Particle size analysis of *P*(AM-*co*-AA) SPH was measured using image analyzer (Leica, England).

RESULTS AND DISCUSSION

Synthesis of Superporous Hydrogel and Incorporation of Carvedilol

After dehydration with ethanol, drying, and size reduction, the SPH looked like hard white granules. Particle size analysis of the resultant powder showed a mean diameter of 0.19±0.06 mm. Incorporation of carvedilol into *P*(AM-*co*-AA) SPH changed its texture into softer granules.

Evaluation of *P*(AM-*co*-AA) SPH

Responses and their regression equations as shown in Tables II and III were used to produce response surface plots to evaluate the studied parameters.

Swelling Studies

There was a significant increase in volume swelling ratio at 45 min upon increasing *P*(AM-*co*-AA) SPH amount ($p<0.0002$). Carvedilol within the designed SNEDDS presented a viscous structure which filled the capillary channels of the hydrogel. Upon contact with water, it blocked the passages of water through the capillary channels and decreased further penetration of water into the superporous hydrogel and contributed to a decrease in the weight swelling ratio of SPH with higher drug/polymer ratio (10). Treating SPH with HCl decreased the volume swelling ratio ($p<0.0001$). HCl treatment hydrolyzed the amide group in SPH ($–CONH_2 \rightarrow –COOH$), facilitating H-bond interaction between it and other existing –COOH groups in the same molecule. Increasing the interaction between the SPH segments may contribute to a decrease in the volume swelling ratio. Figure 1 shows presence of an interaction between the two parameters in the factorial design which may contribute to unexpected results

Estimation of Drug Loading

Increasing the amount of hydrogel was accompanied with increased amount of added HCl during formulation. That led to loss of carvedilol SNEDDS during the formulation step, which made a significant decrease in % carvedilol upon increasing *P*(AM-*co*-AA) SPH ($p=0.0021$) or increasing HCl ($p=0.0003$). Figure 2 shows an interaction between the two parameters used to test their effect on drug loading.

In Vitro Release Studies

There was a nonsignificant increase in % carvedilol released after 45 min upon increasing *P*(AM-*co*-AA) SPH amount as shown in Fig. 3. The swelling rate was not the only factor that affected the release. Other factors such as diffusion of carvedilol also affected the release (11). At a lower drug/polymer ratio, carvedilol SNEDDS may be bounded to the hydrogel inner structure in a stronger way, leading to a decrease in its diffusion.

The significant decrease in % carvedilol released after 45 min upon increasing HCl treatment may be a due to the decrease in swelling ratio, while the significant increase in % carvedilol released upon further increase in HCl may be explained by the increase in the mechanical strength of the hydrogel due to treatment with HCl (10). Increased hydrogel strength prevents the interconnected channel structure from collapsing and, therefore, facilitates carvedilol SNEDDS diffusion from these well-structured channels after swelling.

Morphological Analysis of Superporous Hydrogels

Morphological analysis of superporous hydrogel was done using SEM, and the results are presented in Fig. 4. Non-medicated *P*(AM-*co*-AA) SPH showed smooth surface, while carvedilol *P*(AM-*co*-AA) SPH showed corrugated surface containing some pores. This corrugation reflects the entrapment of the internal interconnected channels to the SNEDDS/carvedilol. Different samples of *P*(AM-*co*-AA) SPH were allowed to swell in 0.1 N HCl and subsequently subjected to lyophilization. Lyophilized *P*(AM-*co*-AA) SPH showed well-structured interconnected channels. These channels were retained after formulation, indicating that the formulation technique did not affect the internal structure of SPH.

CONCLUSION

During the preparation of superporous hydrogel containing carvredilol/SNEDDS, the amount of 0.1 N HCl affected its swelling, carvedilol content, and carvedilol release. Although SPH amount had no effect on carvedilol release, it affected both its swelling behavior and carvedilol content. Further studies are indicated for potential use of SPH as a solid carrier in different pharmaceutical applications. The SPH can carry different types of drugs being subjected to different solubilization or complexation techniques. These particles can also be coated with polymer to formulate enteric coated of controlled release particles.

REFERENCES

1. Peppas NA, Mikos AG. Hydrogels in medicine and pharmacy. Boca Raton: CRC; 1986.
2. Park K. Superporous hydrogels for pharmaceutical & other applications; 2002. http://www.drugdeliverytech.com/cgi-bin/articles.cgi?idArticle=60.
3. Kroupova J, Horak D, Pachernik J, Dvorak P, Slouf M. Functional polymer hydrogels for embryonic stem cell support. J Biomed Mater Res B Appl Biomater. 2006;76(2):315–25.
4. Dorkoosh FA, Broekhuizen CA, Borchard G, Rafiee-Tehrani M, Verhoef JC, Junginger HE. Transport of octreotide and evaluation of mechanism of opening the paracellular tight junctions

using superporous hydrogel polymers in Caco-2 cell monolayers. J Pharm Sci. 2004;93(3):743–52.
5. Ratner BD, Hoffman AS. Synthetic hydrogels for biomedical applications. Washington: American Chemical Society; 1976.
6. Omidian H, Rocca JG, Park K. Elastic, superporous hydrogel hybrids of polyacrylamide and sodium alginate. Macromol Biosci. 2006;6(9):703–10.
7. Kabra BG, Gehrke SH. Rate-limiting steps for solvent sorption and desorption by microporous stimuli-sensitive absorbent gels. Washington: American Chemical Society; 1994.
8. Chen J, Park H, Park K. Synthesis of superporous hydrogels: hydrogels with fast swelling and superabsorbent properties. J Biomed Mater Res. 1999;44(1):53–62.
9. Qiu Y, Park K. Superporous IPN hydrogels having enhanced mechanical properties. AAPS PharmSciTech. 2003;4(4):E51.
10. Chen J, Park K. Synthesis and characterization of superporous hydrogel composites. J Control Release. 2000;65(1–2):73–82.
11. Di Colo G, Baggiani A, Zambito Y, Mollica G, Geppi M, Serafini MF. A new hydrogel for the extended and complete prednisolone release in the GI tract. Int J Pharm. 2006;310(1–2):154–61.