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Short communication

Preparation and *in vitro* characterization of non-effervescent floating drug delivery system of poorly soluble drug, carvedilol phosphate

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The objective of the study was to enhance the solubility of carvedilol phosphate and to formulate it into non-effervescent floating tablets using swellable polymers. Solid dispersions (SD) of carvedilol were prepared with hydrophilic carriers such as polyvinylpyrrolidone and poloxamer to enhance solubility. Non-effervescent floating tablets were prepared with a combination of optimized solid dispersions and release retarding polymers/swellable polymers such as xanthan gum and polyethylene oxide. Tablets were evaluated for physicochemical properties such as hardness, thickness and buoyancy. SD prepared with the drug to poloxamer ratio of 1:4 by melt granulation showed a higher dissolution rate than all other dispersions. Formulations containing 40 mg of polyethylene oxide (C-P40) and 50 mg xanthan gum (C-X50) were found to be best, with the drug retardation up to 12 hours. Optimized formulations were characterized using FTIR and DSC and no drug and excipient interactions were detected.

Keywords: carvedilol phosphate, solid dispersion, non-effervescent, floating tablets

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Carvedilol phosphate is a non-selective beta-blocker, prescribed for the treatment of angina, hypertension and congestive heart failure. The reported systemic bioavailability of carvedilol phosphate is 24 % after oral administration (1). The drug reaches peak plasma concentration in 1–2 h with an elimination half-life of 7 to 10 h (1, 2). This drug has a narrow absorption window in the upper gastrointestinal tract and it would benefit from a gastroretentive delivery system.

Floating drug delivery system (FDDS) is a gastroretentive system that can be effervescent or non-effervescent. Wu *et al.* (3) prepared floating sustained release tablets of nimodipine using HPMC and PEG 6000. Prior to formulation of floating tablets, nimodipine was incorporated into a poloxamer-188 solid dispersion, whereafter it was directly compressed into floating tablets. It was observed that by increasing the HPMC and decreasing

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the PEG 6000 content, a decline in *in vitro* release of nimodipine occurred. Shilpa *et al.* (4) formulated a bilayer floating tablet of carvedilol phosphate using *Ocimum basilicum* mucilage and hypromellose. The release rate and floating characteristics were effectively altered by varying the polymer to gas-generating agent ratio. Swelling polymers and the gas-generating agent produced stable persistent floatation. The results showed that floating tablets are a feasible approach for sustained release preparation of carvedilol phosphate. Xanthan gum and polyethylene oxide (PEO) were found to have the potential in development of FDDS of various drugs with floating time of 12 hours and 98 % drug release (5–7). Even though, research findings on the floating drug delivery of carvedilol phosphate are available, majority of them are effervescent systems only. In the present research, the authors try to explore the non-effervescent floating drug delivery system of carvedilol phosphate without using any gas generating agent. Swellable polymers such as PEO and xanthan gum and matrix ballooning inducers such as crospovidone were used in the formulation, which may lead to floating of the carvedilol phosphate dosage form in gastric medium.

Poor solubility of carvedilol phosphate in acidic pH was enhanced by preparing solid dispersions (SDs) with poloxamer and polyvinylpyrrolidone (PVP) (8, 9). In the present study, comparisons between the two carriers in different solid dispersions (obtained by solvent evaporation and melt granulation) were investigated.

EXPERIMENTAL

Materials

Carvedilol phosphate was purchased from Sree Sai Chemicals, India. Poloxamer 188, xanthan gum, polyvinylpyrrolidone (PVP K30), polyethylene oxide WSR 303 (Polyox® WSR 303), lactose and magnesium stearate was purchased from Labchem Sdn Bhd. Malaysia. Other materials used were of analytical grade.

Preparation of solid dispersions

The SD formulations were prepared by the solvent evaporation and melt granulation methods with different drug-to-carrier ratios. Solvent evaporation using drug/carrier (PVP/poloxamer) ratios 1:1, 1:2 and 1:3 and melt granulation using drug/poloxamer ratios 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6.

Solvent evaporation. – Solid dispersions of carvedilol phosphate were prepared with PVP poloxamer in drug-to-carrier ratios of 1:1, 1:2 and 1:3 by the conventional solvent evaporation technique. Carrier solution was prepared by dissolving required quantities in 15 mL of methanol in a beaker under continuous stirring (for 1:1, 1:2 and 1:3 ratios 1, 2 and 3 g of carrier, respectively). An appropriate mass of carvedilol phosphate (1 g) was dissolved in 15 mL of methanol so as to obtain 0.06 % *m*/*V* of drug solution. Both solutions were mixed and stirred until formation of a clear solution. If any precipitation was observed, a volume was adjusted with methanol to make a clear saturated solution. Solution was evaporated at 40–50 °C to obtain a solid mixture and further dried in a desiccator for 24 h to remove residual solvents. Dried mass was collected, sifted through a 60 mesh (250 μm) sieve and packed in a closed container.

Melt granulation. – Accurately weighed poloxamer 188 (for 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 ratios containing 1, 2, 3, 4, 5 and 6 g of poloxamer respectively) was melted at 50–58 °C using a hot plate. The required quantity of drug (1 g at each ratio) was added to the molten mass under continuous stirring until it dispersed completely. The dispersion was then solidified by cooling in an ice bath for 10–15 min. Resultant product was placed in a desiccator for 24 h, collected, sifted through a 60 mesh (250 μm) sieve and packed in a closed container.

Due to the high melting point of PVP (150 °C), melt granulation was not feasible with PVP.

Physical mixtures were prepared by simple geometric mixing of two pure solid components with a spatula, followed by sieving through a sieve 60 (250 μm).

Characterization of SDs

Content uniformity. – Accurately weighed SDs were dissolved in 15 mL of methanol and made up to 100 mL with 0.1 mol L^{-1} HCl. The solution was further diluted with 0.1 mol L^{-1} HCl until it reached a drug concentration of 10 mol L^{-1} and measured for drug content spectrophotometrically at 241 nm (Perkin Elmer double beam UV-Vis spectrophotometer, Perkin Elmer, USA)

In vitro *dissolution studies.* – The release of carvedilol phosphate from SDs was investigated using a dissolution tester (paddle type) (Electrolab, India) according to USP 2011, Revision bulletin (10). SDs equivalent to 10 mg of the drug were added to the dissolution medium (900 mL of 0.1 mol L^{-1} HCl), maintained at 37 ± 0.5 °C at a speed of 50 rpm. A 5-mL aliquot was withdrawn at regular intervals (5, 10, 20, 30, 45 and 60 min) and replaced with the same volume of fresh dissolution medium. The obtained samples were filtered and measured spectrophotometrically at 241 nm.

Preparation of non-effervescent floating tablets

Direct compression method was followed for the preparation of non-effervescent floating tablets of carvedilol phosphate. Required quantities of solid dispersion and other excipients as mentioned in Table I were weighed accurately, and sifted through a 40 mesh (420 μm) separately. Solid dispersion was geometrically mixed with PEO/xanthan gum until a homogeneous blend was achieved. Crospovidone was then added to the above blend, followed by magnesium stearate (1 %, *m*/*m*). The flow property of the final blend was found to be satisfactory to allow the mixture to be directly compressed into tablets on a 10-station rotary tablet punching machine (M/s. Cadmach Machinery, Co. Pvt. Ltd., India) using 8-mm round plain punches and hardness of 3–4 kg cm^{-2}.

Characterization of floating tablets

Five tablets were randomly selected and measured for hardness using a Monsanto hardness tester (Campbell Electronics, India). Five tablets were randomly selected and measured for thickness with a vernier caliper (Mitutoyo, Japan) (11).

In vitro *buoyancy studies.* – Tablets were placed in a dissolution vessel containing 900 mL of 0.1 mol L^{-1} HCl. The time taken for the tablet to rise to the surface of the dissolution

Table I. Composition of non-effervescent floating tablets of carvedilol phosphate

Ingredient (mg)	Formulation code					
	C-P30	C-P40	C-P50	C-X25	C-X40	C-X50
Carvedilol phosphate solid dispersion[a]	54.5	54.5	54.5	54.5	54.5	54.5
Polyethylene oxide	30.0	40.0	50.0	–	–	–
Xanthan gum	–	–	–	25.0	40.0	50.0
Crospovidone	64.0	54.0	44.0	50.0	54.0	44.0
Lactose	–	–	–	19.0	–	–
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Total mass (mg)	150	150	150	150	150	150

[a] 54.5 mg of drug was taken based on the content uniformity test of the SDs
C-P (carvedilol phosphate-PEO-crospovidone)
C-X (carvedilol phosphate-xanthan gum-crospovidone)
PEO – polyethylene oxide WSR 303

medium (floating lag time) and total duration for the tablet to remain on the surface (total floating time) were recorded (11).

In vitro *dissolution studies. – In vitro* release of carvedilol phosphate from the floating tablets was studied using a dissolution tester (paddle type) (Electrolab, India) in 900 mL of 0.1 mol L^{-1} HCl, maintained at 37 ± 0.5 °C at a speed of 50 rpm for 12 hours. The release of carvedilol phosphate was measured by withdrawing 5-mL aliquots at regular intervals (0.5, 1, 2, 4, 6, 8, 10, 12 h) and replacing the same volume with fresh dissolution medium. The withdrawn samples were filtered and analyzed spectrophotometrically at 241 nm.

Fourier transform infrared spectroscopy (FTIR)

FTIR studies were performed on the drug, poloxamer, SD, xanthan gum, PEO and optimized tablets. Samples were analyzed by the potassium bromide pellet method; pellets had been prepared by gently mixing 1 mg of the sample with 200 mg of potassium bromide. The spectra were scanned using an IR spectrophotometer (Shimadzu, FTIR 8700, Japan) in the region between 4000 and 400 cm^{-1}.

Differential scanning calorimetry (DSC)

DSC analyses of the drug, poloxamer, SD, xanthan gum, PEO and optimized tablets were carried out on a Mettler Toledo DSC (Mettler-Toledo AG, Switzerland). Samples (3–10 mg) were heated under a nitrogen atmosphere in an aluminium crucible at a heating rate of 10 °C min^{-1} over the temperature range of 0 to 200 °C.

RESULTS AND DISCUSSION

In vitro *dissolution of solid dispersions*

The results of *in vitro* dissolution tests are shown in Table II. Dissolution of pure drug was low with only 47.7 % of drug release within 1 hour. There were no significant changes in the dissolution profile of carvedilol phosphate physical mixtures compared to pure drug. All the SDs revealed improved dissolution of carvedilol phosphate compared to the pure drug. On increasing the quantity of poloxamer/PVP, the SDs revealed an increased dissolution rate of carvedilol phosphate for both techniques (solvent evaporation and melt granulation). The highest dissolution rate was observed at the drug-to-carrier ratio of 1:3. The order of increase in the dissolved drug profile from SDS was C-PVP SE < C-POL SE < C-POL MG.

Table II. Percentage of drug released from the prepared SDs, physical mixtures and pure drug

Formulation	Cumulative drug released (%) after (min)[a]					
	5	10	20	30	45	60
Carvedilol phosphate	14.4 ± 0.6	23.5 ± 1.00	29.4 ± 1.45	35.2 ± 1.41	43.0 ± 1.24	47.7 ± 0.99
Physical Mixture (C-PVP 1:3)	16.7 ± 0.9	26.2 ± 0.61	32.4 ± 0.76	39.8 ± 0.45	47.5 ± 0.23	54.1 ± 0.12
Physical Mixture (C-POL 1:4)	22.8 ± 0.1	34.1 ± 0.34	48.4 ± 0.18	55.9 ± 0.52	60.1 ± 0.29	62.7 ± 0.26
C-PVP SE (1:1)	56.0 ± 1.0	58.4 ± 1.56	62.0 ± 0.28	64.1 ± 2.19	66.2 ± 1.70	67.0 ± 1.59
C-PVP SE (1:2)	67.0 ± 1.8	68.5 ± 0.14	69.6 ± 0.69	70.0 ± 1.27	71.4 ± 1.55	72.6 ± 1.05
C-PVP SE (1:3)	70.9 ± 0.6	78.3 ± 0.85	78.5 ± 1.13	79.0 ± 0.71	79.2 ± 0.61	79.4 ± 0.49
C-POL SE (1:1)	46.4 ± 1.7	65.8 ± 2.12	73.5 ± 1.91	74.4 ± 1.27	75.2 ± 0.99	75.7 ± 1.26
C-POL SE (1:2)	72.0 ± 0.3	78.0 ± 0.57	78.6 ± 0.71	79.1 ± 0.91	79.8 ± 0.28	80.2 ± 0.15
C-POL SE (1:3)	72.6 ± 1.4	82.5 ± 1.57	83.4 ± 1.27	83.9 ± 1.24	84.3 ± 0.42	84.5 ± 0.28
C-POL MG (1:1)	54.0 ± 0.6	71.3 ± 1.13	74.0 ± 0.80	75.3 ± 0.57	76.2 ± 0.21	78.9 ± 1.07
C-POL MG (1:2)	78.4 ± 0.5	80.2 ± 1.70	81.3 ± 0.42	81.9 ± 0.48	82.4 ± 0.64	83.1 ± 0.39
C-POL MG (1:3)	85.2 ± 0.7	89.4 ± 2.26	89.7 ± 2.10	90.0 ± 2.55	90.7 ± 1.84	90.9 ± 1.87
C-POL MG (1:4)	90.1 ± 0.1	92.8 ± 0.53	93.3 ± 1.12	93.5 ± 1.30	94.4 ± 1.26	95.6 ± 1.70
C-POL MG (1:5)	79.8 ± 1.2	87.9 ± 1.47	88.1 ± 1.19	88.6 ± 1.02	90.6 ± 0.92	95.6 ± 1.13
C-POL MG (1:6)	70.5 ± 1.8	87.0 ± 1.32	87.3 ± 1.20	87.9 ± 1.24	90.1 ± 1.61	94.6 ± 1.41

[a] Mean ± SD, $n = 3$.
SE – solvent evaporation
MG – melt granulation
PVP – polyvinyl pyrrolidone (PVP K30)
POL – poloxamer 188

Possible explanations for the increased dissolution rates from SDs include the solubilization effect of the carrier, improved drug wettability and reduced drug particle size (12). Based on the results, the melt granulation method was found to be suitable for solid dispersion preparation using poloxamer. However, the percentage of drug release at the end of 1 hour was found to be only 90.9 % with the C-POL MG (1:3) formulation. Therefore, higher drug-to-poloxamer ratios (1:4, 1:5, 1:6) were used in melt granulation. Comparison of the dissolution profiles is given in Table II. C-POL MG (1:4), C-POL MG (1:5) and C-POL MG (1:6) showed maximal cumulative drug release of 95.6, 95.4 and 94.6 %, respectively, with similar drug release patterns suggesting that the increasing of the drug-to-poloxamer ratio above 1:4 did not increase the release rate of the drug. This might be due to formation of a carrier layer around the drug particles, which may not allow the drug to come out of the dispersion (13). Formulation C-POL MG (1:4) was selected as the optimized batch to prepare tablets.

Characterization of floating tablets

Physical characteristics of the prepared tablets are shown in Table III. All the formulations were found to be of good quality.

The *in vitro* buoyancies of the tablets are shown in Table III. The floating lag time of the xanthan gum and PEO formulations was lower than 10 and 30 s, respectively. The polymer (either xanthan gum or PEO) and crospovidone swell in contact with gastric fluids and attain a bulk density of less than 1; therefore they floated on the gastric fluid (14). The swollen matrix imparts buoyancy to the dosage form. It was observed that all tablet formulations floated longer than 12 h, excluding formulations C-X25 and C-X40 which disintegrated in 2 and 6 hours, respectively. These might be due to the high amount of crospovidone in the formulations and rapid hydration of xanthan gum (15).

Table III. Physical parameters of carvedilol phosphate floating tablets

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Floating lag time (s)	Total floating time (h)
C-P30	3–4	2.98 ± 0.19	30 ± 1.3	> 12
C-P40	3–4	2.97 ± 0.08	31 ± 1.0	> 12
C-P50	3–4	2.98 ± 0.01	30 ± 1.1	> 12
C-X25	3–4	2.97 ± 0.18	10 ± 0.5	< 2
C-X40	3–4	3.00 ± 0.20	9 ± 0.8	< 6
C-X50	3–4	3.10 ± 0.34	9 ± 0.9	> 12

Mean ± SD; $n = 3$.

In vitro *drug release*

The *in vitro* drug release data is shown in Fig. 1 for all six tablet formulations. Release profiles of different formulations show that C-P30 showed complete drug release within 10

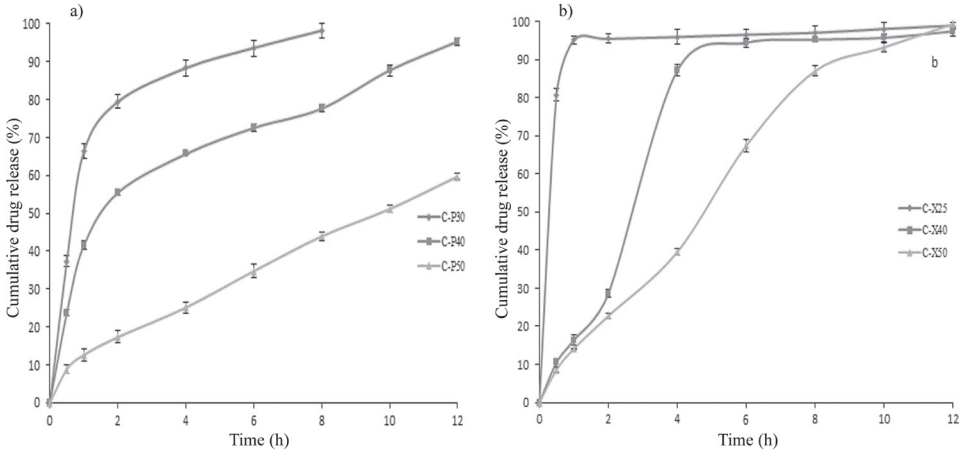

Fig. 1. Dissolution data of: a) PEO formulations, b) xanthan gum tablets (mean ± SD, n = 3).

hours. Formulations C-P40, C-X25, C-X40 and C-X50 released maximum drug at the end of 11, 1, 4 and 12 hours, respectively. The drug release was retarded with the increase in polymer concentration. Formulation C-P50 showed the lowest drug release (59.7 ± 0.4 %) after 12 hours. This may be due to higher polymer concentration to induce formation of larger viscous gel layer, thus increasing the diffusional path length of the drug (16). Formulation C-X25 shows burst release of 80.7 % of the drug in 30 min, which may be because erosion occurred before complete swelling could take place. Drug release from the matrix is dependent on the polymer swelling, drug diffusion and matrix erosion (15).

FTIR

Fig. 2 gives the spectra of the pure drug, poloxamer, SD, xanthan gum, PEO and optimized tablets. FTIR spectrum of carvedilol phosphate showed characteristic bands at 3416.05 (overlapping of –OH and –NH stretch), 3005.2 (aromatic C-H stretch) 1504.53 (aromatic C=C stretch) and 1253.77 cm^{-1} (aromatic C-N stretch). Poloxamer exhibited absorption peaks at 3423.76 (H-bonded O-H stretch), 2889.46 (C-H aliphatic stretch) and 1112.96 cm^{-1} (C-O stretch). The SD spectrum showed disappearance of the peak at 3416.05 cm^{-1} and the presence of all other carvedilol phosphate peaks with decreased intensity compared to the drug alone. Optimized C-X50 and C-P40 tablets showed same peaks as SD with slight variation. No additional peak was observed to indicate the absence of any chemical interaction between the drug and poloxamers. Optimized formulations exhibited the characteristic peaks of carvedilol phosphate with no additional peaks observed in the spectra, indicating retention of chemical identity of carvedilol phosphate, as shown in Fig. 2. However, the intensity of peaks corresponding to the drug was reduced or peaks were broadened in the formulations possibly due to the encapsulation of the drug with the carrier, *i.e.*, poloxamer in melt granulation and possibly due to addition of other excipients. The FTIR data indicate the absence of chemical interaction between carvedilol phosphate and the excipients used.

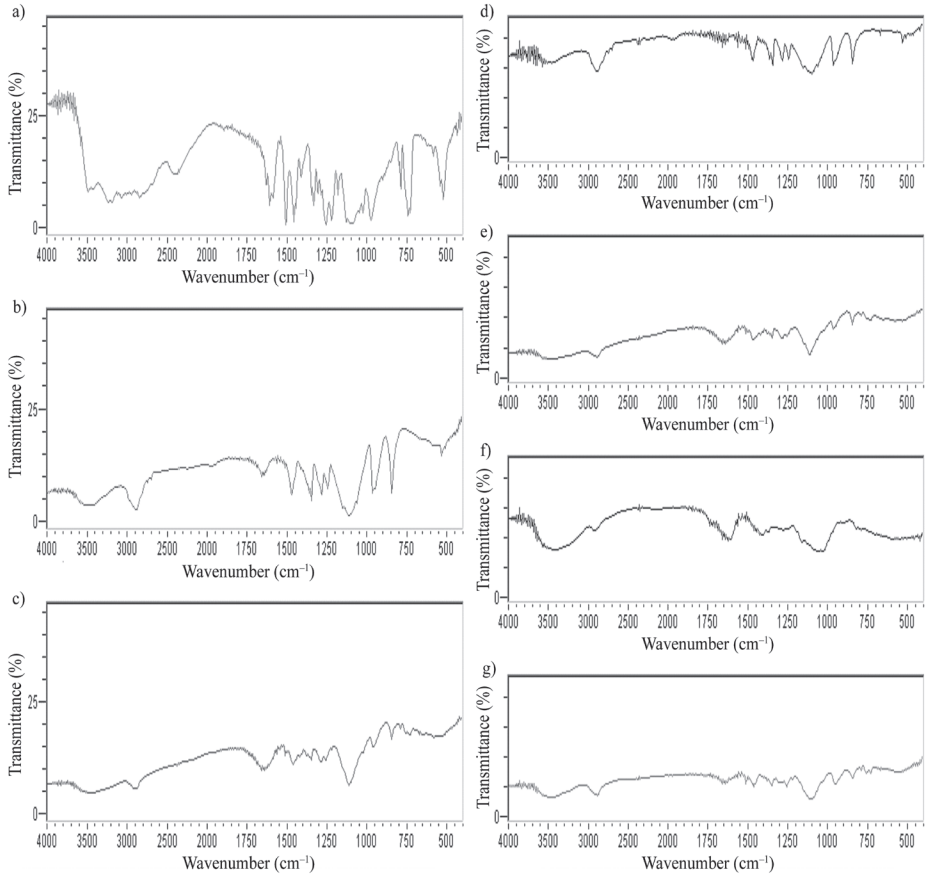

Fig. 2. FTIR spectra of: a) carvedilol phosphate, b) poloxamer 188, c) SD with carvedilol phosphate: poloxamer 188 ratio 1:4, d) xanthan gum, e) optimized C-X50 tablet, f) PEO, g) optimized C-P40 tablet.

DSC

Thermograms of the pure drug, poloxamer, SD, xanthan gum, PEO and optimized tablets are presented in Fig. 3. Carvedilol phosphate showed a sharp melting endotherm at 159.1 °C, while poloxamer 188 showed a melting endotherm at 54.7 °C. Thermograms of SD (1:4) showed decreased peak intensity of carvedilol phosphate (155.3 °C). The melting peak of poloxamer in SD was observed at a slightly lower temperature (54.5 °C) than that of pure poloxamer 188. Reduction in intensity and shifting of the sharp melting peak of the drug in SD indicate that the degree of crystallinity was considerably reduced and the drug may have been convert to amorphous form (8). The DSC peaks revealed that there was no chemical interaction between the drug and excipients used.

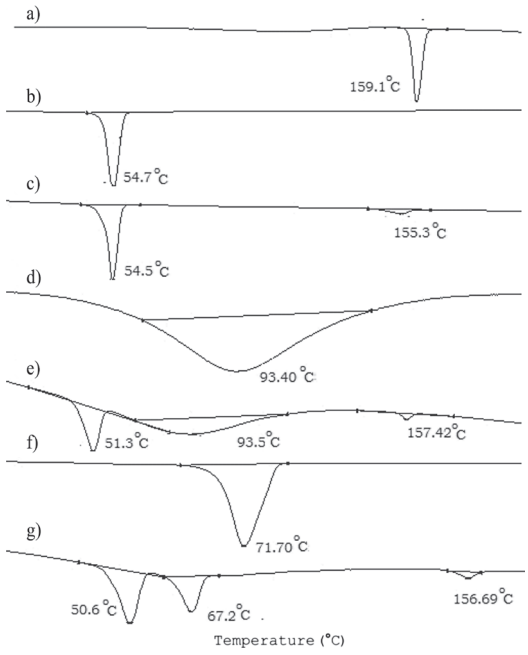

Fig. 3. DSC thermograms of: a) carvedilol phosphate, b) poloxamer 188, c) SD with carvedilol phosphate: poloxamer 188 ratio 1:4, d) xanthan gum, e) C-X50 floating tablet, f) PEO, g) C-P40 floating tablet.

CONCLUSIONS

Solid dispersion of carvedilol phosphate-poloxamer prepared with melt granulation is a promising method for enhancing the solubility of carvedilol phosphate. Xanthan gum and PEO are suitable polymers for the development of non-effervescent floating tablets of carvedilol phosphate. Drug release from the prepared floating tablets exhibited sustained release of the drug over a prolonged period of time. Future studies such as *in vivo* investigations are recommended to evaluate the gastric retention of selected floating tablets. Further studies are also recommended to evaluate the stability of formulations.

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