ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
www.ijptonline.com
Research Article

INTRINSICALLY FLOATING GASTRORETENTIVE TABLETS OF SALBUTAMOL SULPHATE USING DIFFERENT SUBLIMABLE/RELEASE RETARDING MATERIALS: A COMPARATIVE STUDY

May Saab*, Mohamed Issa[2], Wael Samy[3], and Hoda El-Maradny[1]
*Lecturer at the department of Pharmaceutical Technology, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon.
Email: saabk.may79@yahoo.com, saabk.may79@bau.edu.lb
[1]Head of Depatment of Pharmaceutical Technology, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon.
Email: h.almaradni@bau.edu.lb
[2]Assistant Professor at the Departement of Pharmacy Practice, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon.
Email: mohamed.issa@bau.edu.lb
[3]Head of Department of Industrial Pharmacy, Faculty of Pharmacy, Alexandria University, Alexandia. Egypt,
Email: wsamy73@yahoo.com

Received on 22-06-2015 *Accepted on 20-07-2015*

Abstract

Aim: The current study aimed to formulate porous floating gastroretentive tablets containing salbutamol sulphate (SS), using sublimation technique. Different formulations of SS porous tablets were prepared using hydroxypropylmethyl cellulose (HPMCK15M) or polyethylene oxide (PEOWSR301) as release-retarding polymers, and L-menthol, camphor or ammonium carbonate as sublimable materials.

Methods: All tablets were prepared by direct compression technique followed by sublimation. The possibility of any drug-excipient interaction was investigated by differential scanning calorimetry (DSC) and fourrier transform infrared (FTIR). The porosity of the tablets was visualized using scanning electron microscope (SEM). Moreover, the effect of porosities and polymers on the physicochemical properties, swelling behavior and drug release profile of tablets were also studied.

Results: After sublimation, tablets revealed a more porous morphology for menthol and camphor containing formulations, compared to ammonium carbonate. All porous tablets floated for over 24 hours with no floating lag time, except for ammonium carbonate that floated for 8 hours. Drug release profiles were affected by changing the type of polymer in the formulations, with a more sustained effect for HPMC-containing tablets. Drug release kinetics for all

formulations demonstrated the best fit for Korsmeyer-Peppas model with n values ranging from 0.454-0.686, indicating an anomalous non fickian transport mechanism.

Conclusion: Based on the results obtained, the formula containing HPMC and menthol (F1) was shown to be the optimum formula, requiring a minimal time for complete sublimation, having a highly porous stucture and providing a sustained drug release for over 10 hours.

Keywords: Floating tablets, Gastroretentive, Salbutamol sulphate, Sublimation.

Introduction

Sustained drug delivery systems via oral route have gained much interest for many years, as it is considered the most common and convenient way for drug administration and patient compliance. However, the bioavailability of oral drugs can be influenced by many variables, such as drug solubility and release profile, transit time through the gastrointestinal tract, and main absorption site [1]. A prolonged gastric residence time is favorable for drugs that show maximum absorption from stomach or upper part of small intestine, in order to enhance their bioavailability. Therefore, gastroretentive (GR) drug delivery systems are quite advantageous [2].

Different approaches in developing GR systems have been previously reported, as high density, mucoadhesive, superporous hydrogels, floating and expandable systems [3]. The floating drug delivery systems are able to float on the surface of gastric fluids for an extended period of time, thereby, targeting drug release in stomach and upper gastrointestinal tract [4].

Several techniques were used to formulate floating GR drug delivery systems, namely hollow microspheres using solvent evaporation technique [5], floating matrix tablets using low-density materials such as polypropylene foam powder [6] and multiple-unit floating porous system based on crosslinked calcium-alginate beads [7]. The sublimation technique showed to be one of the best approaches in designing an inherently floating gastroretentive tablets. This technique was first adopted in the development of famotidine floating tablets by Fukuda and Goto [8]. They used menthol as sublimable tablet core that was dry coated by a mixture of mannitol and famotidine. Upon sublimation, they obtained hollow tablets that were dip-coated in a mixture of glyceryl monostearate and lubriwax, where the resultant tablets floated for 6 hours with a sustained drug release profile. Later on, Park et al. [1] developed porous floating tablets, using the sublimation technique. They developed metformin HCl floating tablets, using PEO WSR301 as release controlling polymer, and

camphor as a sublimable material. Upon heating, camphor sublimed resulting in porous low density tablets that floated immedialy for over 24 hours, with a sustained drug release profile. Recently Kesarla et al. [9] developed PEO porous floating tablet of ranitidine HCl using menthol as sublimable material. After sublimation the tablets showed an average floating lag time of 6 seconds and a floating duration of more than 24 hours, accompanied with a controlled drug release profile. However, none of the previous reports on the sublimation technique studied and highlighted the effect of the type of polymer and sublimable material on the physicocemical properties of tablets, and their significance from a technical point of view when considering the time for complete sublimation.

Salbutamol sulphate (SS) is a bronchodilator that is freely soluble in water and has site-specific absorption in stomach and upper part of small intestine. The oral bioavailability of SS is ~40% because of extensive metabolism in the liver and colon [10]. The drug has a short biological half life of 3.8 hours, and thus requires frequent administration [11]. Therefore, SS is considered a good candidate to be formulated in gastroretentive floating tablets.

In the present study we aimed to formulate porous floating tablets of salbutamol sulphate using the sublimation technique, and to investigate the effect of the type of polymer and sublimable material on the physicochemical properties of the resulting tablets and their importance on the sublimation process. Our main goal is to reach both the optimum and time effective approach in formulating porous floating tablets of SS with a sustained drug release profile, in an attempt to reduce its frequency of administration and improve its bioavailability.

Different polymers were employed in GR drug delivery systems [12]. However, hydroxypropylmethyl cellulose (HPMC) and polyethylene oxide (PEO) are considered the most important release-retarding polymers. They are hydrophilic in nature and available in high molecular weights and viscosities, thus, resulting in sustained release patterns [13].Subsequently, PEO WSR 301 and HPMC K15M were used as the release retarding polymers under study, in addition to different sublimable materials (L-menthol, camphor and ammonium carbonate).

Materials and methods

Materials:

Salbutamol sulphate (SS) was gifted from Mediphar laboratories, Beirut, Lebanon.

Polyethylene oxide (PEO WSR 301), L-menthol, camphor and ammonium carbonate were supplied from Sigma Aldrisch, USA.

Hydroxypropylmethyl cellulose (HPMC K15M) was supplied from Alexandria Pharmaceutical Co., Alexandria, Egypt. All other additives and reagents were purchased from Fluka, Germany, and were of analytical grade.

Preparation of floating GR tablets of SS:

Different formulations were prepared using release-retarding polymers (HPMC K15M or PEO WSR 301) and sublimable materials (L-menthol, camphor or ammonium carbonate) (Table I). The ingredients were mixed homogenously, then directly compressed using a single punch tablet press (Vanguard Pharmaceutical Machinery, Inc. USA.) equipped with a 9 mm double concave punch. Tablets hardness were adjusted and ranged between 60.82 and 67.20 N using Erweka hardness tester (MT-62256, Germany).

Compressed SS tablets containing HPMC coupled with menthol or ammonium carbonate were placed for a period of 3 hours in hot air oven (Gallenkamp, England) at a temperature of 80°C to allow complete sublimation of the sublimable material, while camphor required 5 hours for its complete sublimation from HPMC tablets at the same conditions. On the other hand, SS tablets containing PEO were subjected to a lower temperature of 50°C (permitting sublimation of the sublimable material without melting of PEO) for a period of 12 hours for menthol and ammonium carbonate containing tablets and 24 hours for those containing camphor. Tablets weight was measured at regular time intervals till constant weight was obtained, indicating complete sublimation of the sublimable materials (Table I).

Scanning electron microscope (SEM):

Different tablet formulations having different sublimable materials and release retarding polymers were visualized after sublimation using SEM (ASC-2100, Seron technology, Korea). Cross sections of all sample tablets were coated with a thin layer of palladium gold alloy in a Hummer I Sputter coater and imaged.

Differential scanning calorimetry (DSC):

Thermograms of pure drug, sublimable materials, polymers, their physical mixtures and tablets after sublimation, were plotted to detect any possible interactions. Samples (3 mg) were placed in sealed aluminum pans and heated at a rate of 5°C/min under nitrogen atmosphere (flow rate 20 mL/min) in the range of 30°C–250°C and analyzed using Shimadzu differential scanning calorimeter (DSC-60, Japan).

Fourrier transform infrared (FTIR):

FTIR spectra of samples of pure drug, polymers, sublimable materials, physical mixtures and tablets after sublimation, were recorded using a Shimadzu FTIR spectrometer (Model-1601 PC, Japan). Samples were prepared in KBr discs, and the scanning range was from 400 to 4000 cm^{-1}.

Evaluation of physicochemical properties of the formulated tablets:

Drug content:

The prepared tablets were evaluated for their content uniformity, where samples equivalent to 9.6 mg of SS were analyzed spectrophotometrically using Jasco spectrophotometer (V-530, Japan) at 276 nm.

Friability and hardness:

The percentage friability was investigated using Erweka Friabilator (TADR-61823, Germany) and hardness (N) was measured using Erweka hardness tester (MT-62256, Germany).

Density:

The density of the GR tablets (g/cm^3) was calculated as W/V, where W is the weight (mg) of the tablet, and V is the volume (cm^3) of the biconvex tablet that was determined by a geometric approach derived from the following equation [14]:

$$V = \frac{2}{6}\pi h(3a^2 + h^2) + \pi a^2.b$$

Where a is the tablet radius, h is the height of the tablet spherical cap and b is the height of the tablet edge.

The results obtained were the average of three determinations.

Porosity:

The percentage porosity of the tablets obtained after sublimation was determined, from the following equation:

$$\%\ \text{porosity} = [1 - \frac{\rho 2}{\rho 1}] \times 100\ ,$$

Where ρ_1 and ρ_2 are the tablet densities before and after sublimation, respectively.

In vitro floating study:

Tablets from each formulation were placed individually in a 100 ml Nessler tube containing 0.1 N hydrochloric acid and monitored for floating lag time and floating duration time.

Swelling behavior:

Swelling behavior of formulated tablets was carried out in 500 ml 0.1 N hydrochloric acid kept at 37±0.5°C using USP dissolution apparatus II (Jacso, Japan) rotated at 50 rpm. At one-hour intervals, the tested tablets were taken, blotted to remove excess water, and then weighed. The percentage increase in weight was estimated using the following equation:

$$\text{weight gain}(\%) = \frac{\text{Ws} - \text{Wi}}{\text{Wi}} \times 100$$

Where Ws is the weight of the swollen tablet (mg) and Wi is the initial weight of the tablet (mg).

In-vitro release profile:

The release profile of SS from different formulations was studied using the USP dissolution apparatus II. The dissolution test was performed using 500 ml of 0.1 N HCl. kept at 37±0.5 °C and rotated at 50 rpm. Samples, 5 ml each, were withdrawn at the predetermined time intervals. The medium was replenished with 5 ml of fresh dissolution medium each time. The samples were filtered through a millipore filter (0.45 µm) and analyzed spectrophotmetrically at 276 nm.

Release kinetics:

The release data were fitted to different release kinetic models, namely Zero-order, First-order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas models.

Results and Discussion

SEM:

In this study, the influence of sublimation on the tablet morphology was investigated by SEM (figure 1), which showed a porous structure. The pore size was relatively larger for the tablets containing L-menthol (figure 1: a and d), and camphor (figure 1: b and e), compared to that of ammonium carbonate containing tablets (figure 1: c and f) using either HPMC or PEO. This may be attributed to the larger particle size of L-menthol (350 µm) and camphor (400 µm) in the original blend, compared to that of ammonium carbonate (150 µm).

DSC:

Figures 2 and 3 illustrate DSC thermograms of pure drug, polymers, sublimable materials, physical mixtures and tablets after sublimation, using HPMC and PEO, respectively.

SS showed a characteristic sharp endothermic peak at 196.78 °C corresponding to its melting point and indicates the crystalline nature of the drug (figures 2a and 3a). These findings are in agreement with Nouh. et al. [15]. The sublimable materials L-menthol and camphor showed endothermic peaks at 44.45 °C (figures 2c and 3c) and 175.57 °C (figure 2f and 3f), respectively, corresponding to their melting points, whereas ammonium carbonate showed an endothermic peak at 81.78 °C (figures 2i and 3i) indicating its decomposition. Thermogram of HPMC revealed a broad endothermic peak at 63°C (figure 2b), which is attributed to the polymer dehydration [16]. The thermogram of PEO (figure 3b) showed one endothermic event that corresponds to the melting of the crystalline polymer starting at 63°C and reaching its peak at 69.68 °C, with the enthalpy change of 451.61J/g.

The DSC analysis of the physical mixtures of SS and HPMC containing different sublimable materials (figure 2: d, g and j), revealed all the characteristic peaks with negligible change in the melting point of SS, indicating no modification or interaction between the drug and other excipients. However, a reduction in the peak intensity was observed with an enthalpy of less than 5J/g, compared to that of pure drug (157.93 J/g). This reduction in peak intensity was mainly attributed to the dilution effect of the polymer [17].

Tablet samples corresponding to HPMC-based formulations after sublimation (figures 2: e, h and k) revealed the characteristic endothermic peaks of the drug and polymer with the absence of the sublimable material endotherm, confirming the complete sublimation of the latter.

Physical mixtures containing PEO (figures 3: d, g and j), showed a complete absence of SS peaks in the samples, which can be attributed to the molecular dispersion of the drug in the molten polymer [18]. The thermal behavior of PEO containing tablets after sublimation (figures 3: e, h and k) indicated the absence of the sublimable material endotherm.

FTIR:

FTIR spectra of pure drug, polymers, sublimable materials, physical mixtures and powdered tablets after sublimation, using HPMC and PEO, respectively, are shown in figures 4 and 5. IR spectrum of SS (figures 4a and 5a) revealed characteristic peaks at 1506.48 & 1467.97 cm^{-1}, corresponding to C=C stretching in aromatic ring, and at 3143.07 cm^{-1},corresponding to NH stretching, in addition to different peaks ranging from 2454.5 to 2779.33 cm^{-1},corresponding to C-H stretching of the alkyl groups. IR spectra of the physical mixtures, as well as tablets after sublimation, revealed all

the characteristic bands and there was no difference in the drug spectra compared to pure SS. These findings indicated that there was no drug-excipients interaction, thus confirming the results obtained by DSC.

Evaluation of physicochemical properties of the formulated tablets:

Drug content: The drug content of all tablet formulations ranged from 94.7%±1.54% to 106.8%±2.16%, revealing the uniformity of drug distribution.

Friability: The percentage friability was less than 1%, indicating an acceptable limit according to the USP35 specifications.

Hardness: Before sublimation, the hardness of all tablet formulations ranged from 60.82 to 67.20 N, while after sublimation it decreased and ranged from 51.52 to 56.90 N (Table II). The effect of resulting porosity on the hardness of tablets was investigated. Lower hardness were recorded for menthol and camphor containing tablets compared to that of ammonium carbonate-containing tablets, after sublimation. These results are in agreement with our morphological findings where the tablet formulations that had lower hardness were those having larger pores (figure 1: a, b, d and e). Moreover, Park et al.[1] studied the effect of the particle size of camphor on the hardness of tablets after sublimation. Their results indicated that larger inner pores obtained after sublimation of large camphor particles, resulted in a decrease in tablet hardness to a higher extent, compared to smaller inner pores produced by smaller camphor particles after sublimation.

Porosity and density:

The observed porosity played an important role in reducing the density of tablets (Table II). All tablets recorded a reduced density after sublimation, to an extent depending on the percentage porosity obtained. The lowest densities were observed in tablets formulated with menthol (F1 and F4) and camphor (F2 and F5), that produced higher percentage porosities after sublimation (27-30%),compared to tablets formulated with ammonium carbonate (F3 and F6) that produced lower percentage porosities (21-22%).

In-vitro floating behavior:

All tablets had no floating lag time and a floating duration of more than 24 hours except for ammonium carbonate containing tablets that floated for only 8 hours. Kesarla and Goto [9] studied the effect of different amounts of menthol (15-40 mg) on the floating properties of PEO tablets after sublimation. They observed that the floating lag time of the

tablets decreased with an increase in the amount of menthol in the formulation, recording no floating lag time for formulation containing 40 mg menthol. In our study, the amount of sublimable material (50 mg) was quite enough for getting an immediate floating of the tablets.

The floatation of the tablets is mainly attributed to the inherent low density of the porous tablets that ranged from 0.68 to 0.83 g/cm3 (Table II). However, the relatively low duration of floating of ammonium carbonate tablets may be due to the smaller pores obtained after sublimation when compared to menthol and camphor. Such pores may have been filled with water during the tablet swelling resulting in the sinking of the latter. Consequently, the size of pores generated after sublimation is an important parameter when considering the floating duration of the tablets. Therefore, menthol and camphor showed better floating properties compared to ammonium carbonate, by providing larger pores to the tablets after sublimation.

Swelling behavior:

The swelling behavior of the porous HPMC or PEO tablets was not affected by the level of porosity resulting from sublimation of different sublimable materials (figure 6). On the other hand, upon comparing HPMC with PEO porous tablets, the latter showed a remarkably higher swelling of more than 500%. Such difference in the extent of swelling can be explained by the high degree of hydrophilicity of PEO polymer and the relatively lower resistance of its polymeric network structure against water movement when compared to HPMC[19].

These findings are in accordance with those obtained by Todd et al. [20], who compared the swelling properties of PEO and HPMC and noticed a greater hydration of PEO that swelled twice as much as HPMC.

In-vitro Release profile of SS from the formulated tablets:

The effect of porosity on the release profile of the floating tablets was investigated. The results showed an insignificant difference in the release profile of each of HPMC or PEO containing porous tablets (figure 7). The effect of polymers on the drug release profile was also studied. HPMC porous tablets (F1, F2 and F3) showed a sustained drug release, recording about 22% in the first hour and attained about 95% after 10 hours. On the other hand, PEO porous tablets (F4, F5 and F6) showed a faster drug release in the first hour of about 34% and reached 98% after 10 hours. The results are in accordance with Sanjeevani et al. [21], where mebeverine HCl tablets containing PEO swelled quickly to form a weak gel, that was more susceptible to erosion than HPMC. Balazs and Leucuta [13] also studied the release of Diltiazem HCl

from PEO, HPMC, and HPC matrices of comparable viscosities. Diltiazem HCl release from PEO matrices was more rapid and complete than its release from HPMC and HPC matrices.

Based on our findings, the nature of the polymer and its characteristics seemed to have a crucial effect on the drug release profile from the formulated tablets, demonstrating a more sustained effect for HPMC-containing tablets. Furthermore, the sublimation process was faster from HPMC-containing formulae (3-5 hours), compared to that of PEO (12-24 hours) where the relatively lower temperature applied on the latter (50° C) may have played a role in extending the time for complete sublimation through the pathways of the polymer network structure. Therefore, HPMC tablet formulations showed to be better than those of PEO from a technical and physicochemical point of view. In earlier reports[1, 9], PEO porous tablets of metformin HCl and ranitidine HCl prepared by sublimation technique proved to have good floating properties and a sustained drug release profile. However, the sublimation process from the tablets was time consuming, reaching 24 hours.

Release kinetics:

In order to investigate the mechanism of drug release kinetics, the experimental data were fitted to zero-order, first order, Higuchi, Hixon-Crowell and korsmeyer-peppas models (Table III).

The results showed that all formulations were best fitted to Korsmeyer-Peppas model recording the highest R^2 values ranging from 0.9953 to 0.9988. The n values for the Peppas model of all porous tablets ranged from 0.454 to 0.686 indicating an anomalous transport mechanism [22]. These results are in accordance with those reported by Sanjeevani et al. [21], where drug release was mainly governed by both drug diffusion through hydrated gel layer of polymer and disentanglement or erosion of the hydrated polymer.

Conclusions

The study has shown that the polymer type has a pronounced effect on the sublimation process and on release profiles of the resulting porous floating tablets, revealing faster sublimation and more sustained effect for HPMC containing formulae compared to that of PEO, thus favoring the selection of HPMC. Moreover, the GR porous tablets of SS obtained by sublimation of menthol or camphor had better floating properties than those obtained by sublimation of ammonium carbonate. However, menthol showed to have an advantage over camphor from a technical point of view during the tablet formulation, as it requires less time for its complete sublimation from HPMC containing tablets (3

hours) when compared to camphor (5 hours). From our findings we can conclude that SS formulation consisting of HPMC and menthol (F1) was the optimum formulation. It offered a time effective approach in formulating highly porous floating tablets that floated for more than 24 hours with a sustained drug release profile. Subsequently, it showed to be a promising gastroretentive drug delivery system to reduce the frequency of administration of SS and to improve its bioavailability.

Table I: Different formulations of Salbutamol Sulfate gastroretentive floating tablets.

Material (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Salbutamol sulphate	9.6	9.6	9.6	9.6	9.6	9.6
HPMC K15M	140.4	140.4	140.4	-	-	-
PEO WSR301	-	-	-	140.4	140.4	140.4
Menthol	50	-	-	50	-	-
Camphor	-	50	-	-	50	-
Ammonium carbonate	-	-	50	-	-	50
Total weight of tablet before sublimation	200	200	200	200	200	200
Total weight of tablet after sublimation	150	150	150	150	150	150

Table II: Physical properties of the formulated tablets.

Formulation code	Before sublimation		After sublimation		
	Hardness(N)	Density (g/cm3)	Hardness(N)	Density (g/cm3)	Mean percentage porosity (%)
F1	62.19±1.47	1.05± 0.013	52.19±1.67	0.73± 0.015	30.48%
F2	65.43±1.67	1.12± 0.017	51.70±1.57	0.79± 0.008	28.18%
F3	62.98±1.96	1.07± 0.008	56.90±1.46	0.83± 0.013	22.43%
F4	67.20±0.59	0.95± 0.007	51.52±1.96	0.68± 0.008	28.42%
F5	63.27±1.28	0.98± 0.012	52.48±1.18	0.71± 0.005	27.55%
F6	60.82±1.47	1.03± 0.006	56.31±1.67	0.81± 0.009	21.36%

Table III: Release kinetics of Salbutamol Sulfate from the prepared tablets.

Formulation code	Zero order		First order		Higuchi		Hixson-Crowel		Korsmeyer-Peppas		
	R^2	K	R^2	K	R^2	K	R^2	K	R^2	K	n
F1	0.9769	8.93	0.9414	0.23	0.9858	30.88	0.9859	0.25	0.9984	19.36	0.454
F2	0.9749	8.98	0.9254	0.25	0.9892	31.12	0.9813	0.26	0.9988	22.18	0.526
F3	0.9701	9.14	0.8525	0.33	0.9924	31.82	0.9647	0.30	0.9953	26.24	0.480
F4	0.9196	7.72	0.9419	0.22	0.9950	27.63	0.9725	0.23	0.9979	33.65	0.686
F5	0.9660	8.98	0.9217	0.27	0.9946	31.35	0.9831	0.27	0.9986	28.06	0.613
F6	0.9951	9.05	0.7603	0.40	0.9956	31.82	0.9518	0.32	0.9976	29.65	0.530

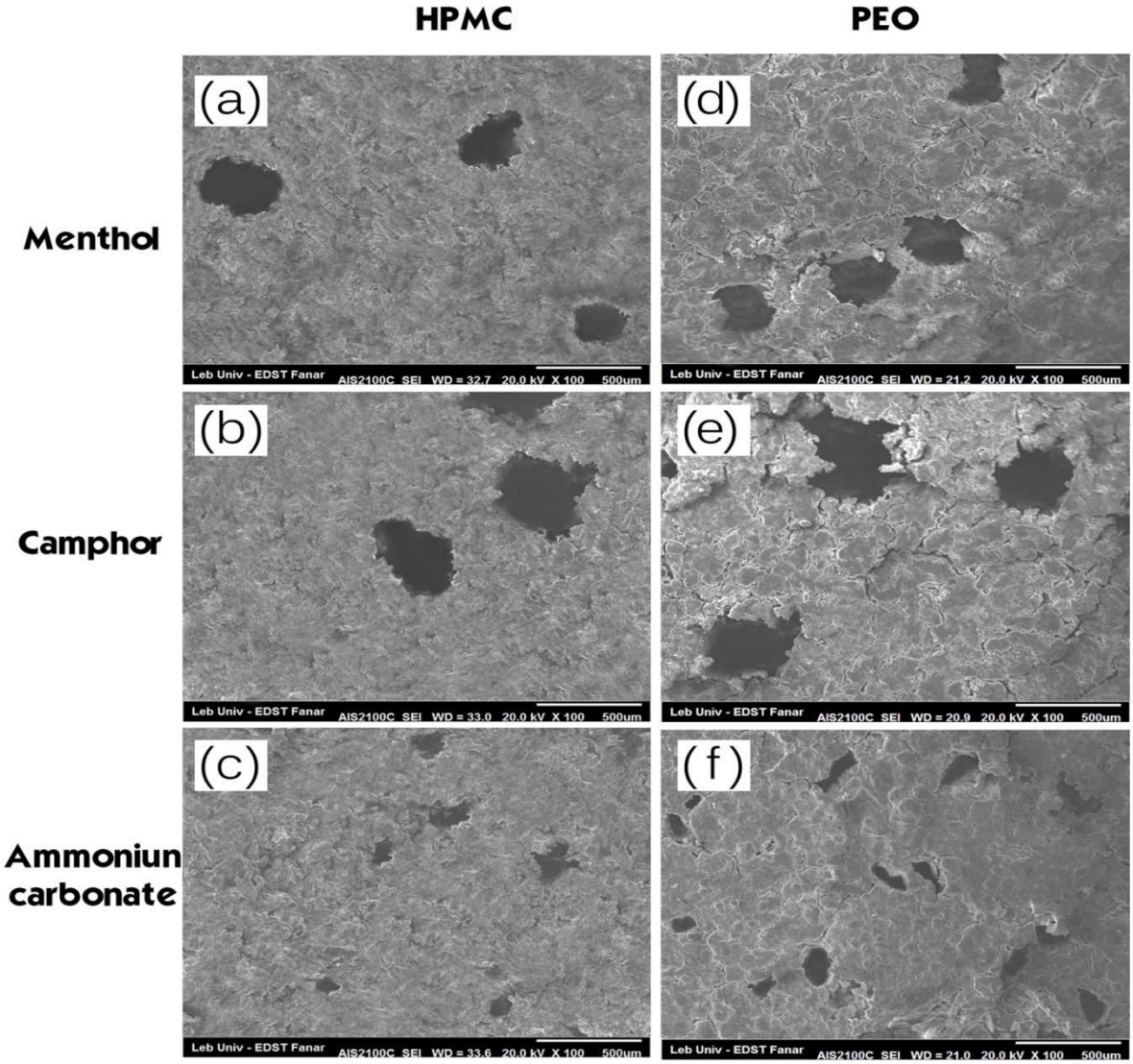

Figure 1: Scanning electron microscope of tablets containing HPMC with menthol (a) , camphor (b), ammonium carbonate (c) or PEO with menthol (d), camphor (e), ammonium carbonate (f), after sublimation.

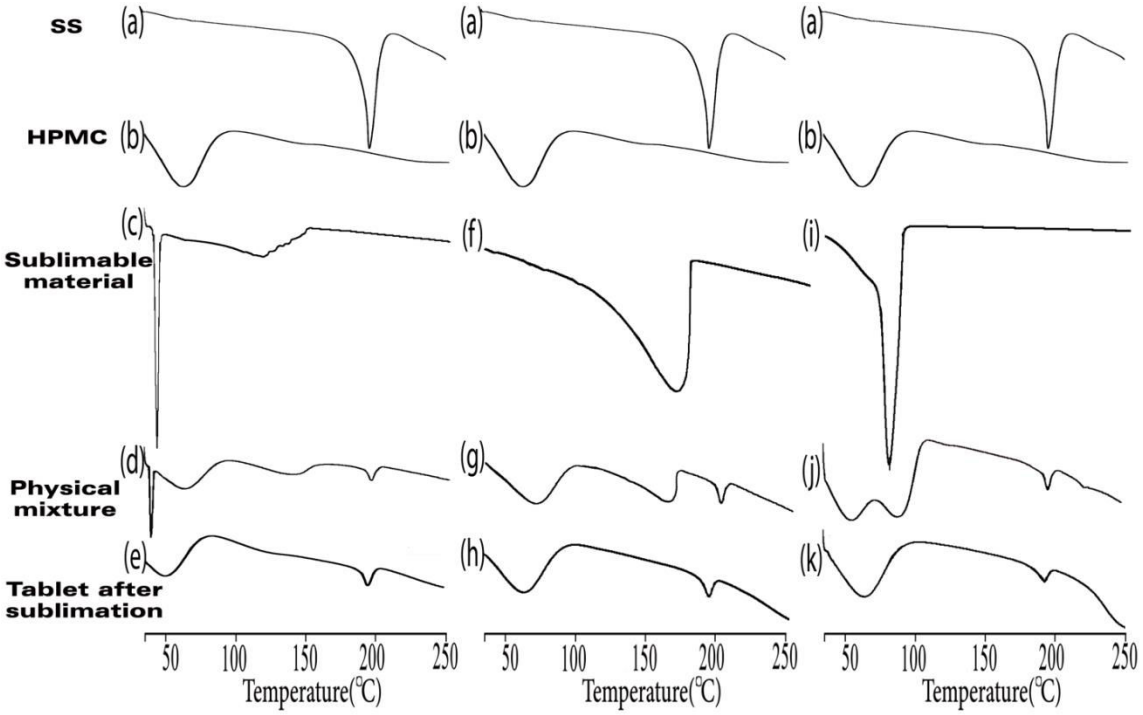

Figure 2: DSC thermograms of SS (a), HPMC (b), menthol (c), camphor (f), ammonium carbonate (i), physical mixture with menthol (d), camphor (g), ammonium carbonate (j), tablets after sublimation of menthol (e), camphor (h), ammonium carbonate (k).

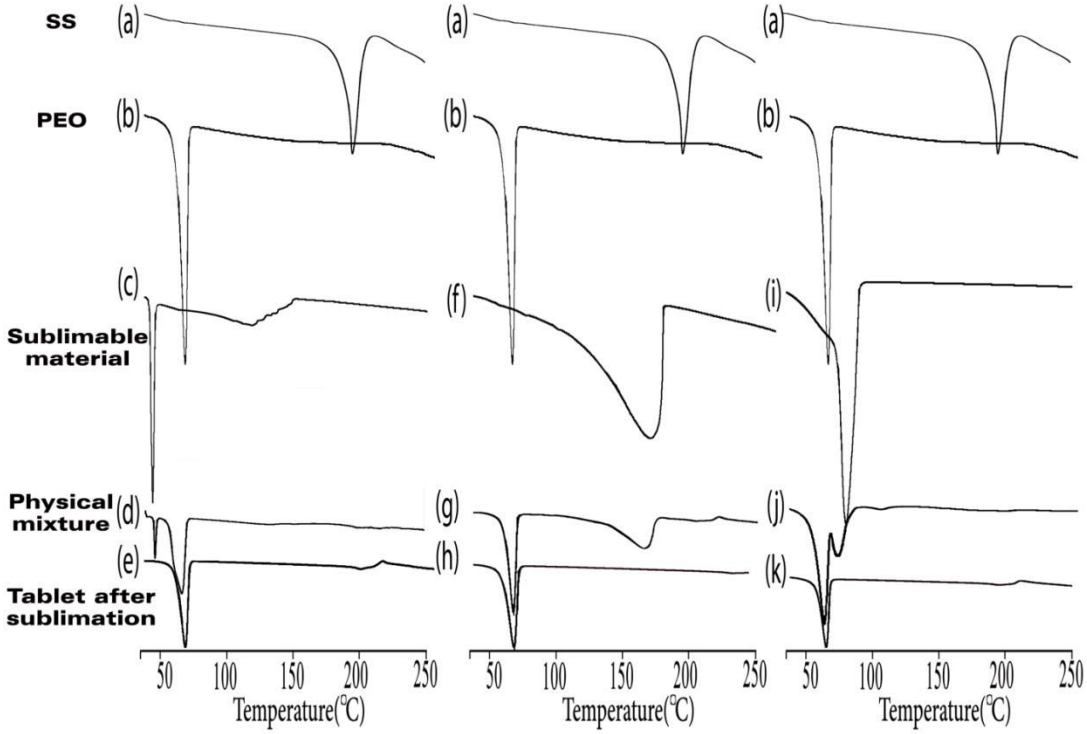

Figure 3: DSC thermograms of SS (a), PEO (b), menthol (c), camphor (f), ammonium carbonate (i), physical mixture with menthol (d), camphor (g), ammonium carbonate (j), tablets after sublimation of menthol (e), camphor (h), ammonium carbonate (k).

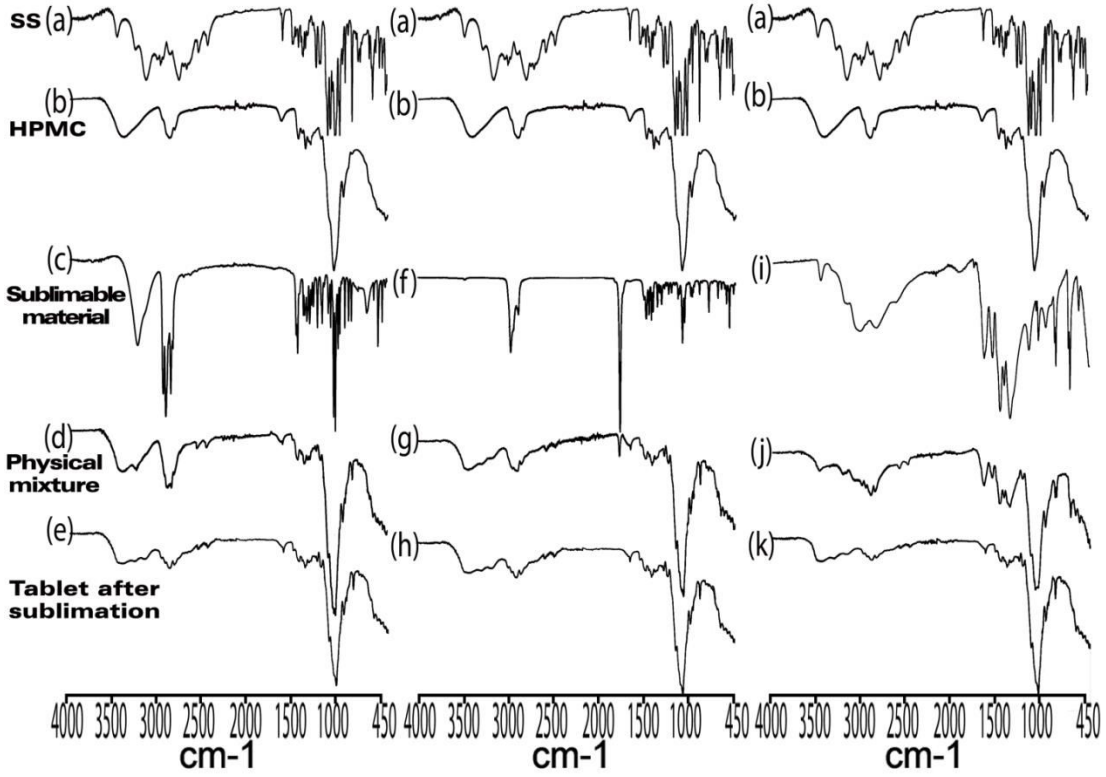

Figure 4: FTIR spectra of SS (a), HPMC (b), menthol (c), camphor (f), ammonium carbonate (i), physical mixture with menthol (d), camphor(g), ammonium carbonate (j), tablets after sublimation of menthol (e), camphor (h), ammonium carbonate (k).

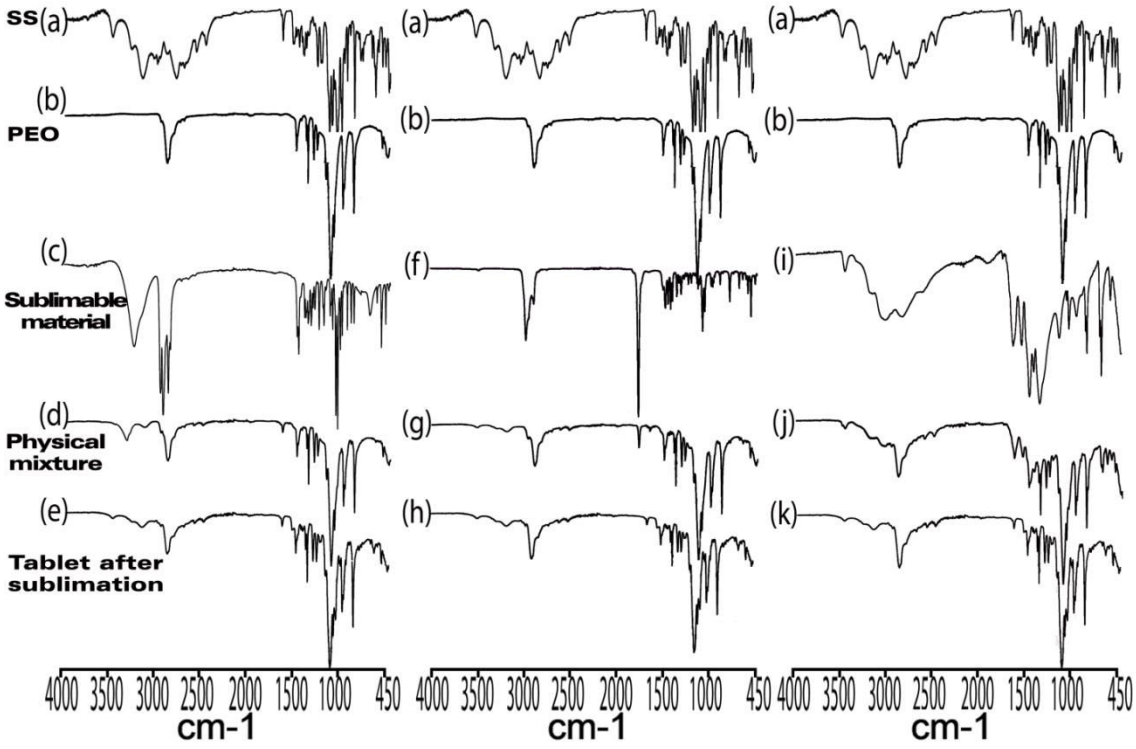

Figure 5: FTIR spectra of SS (a), PEO (b), menthol (c), camphor (f), ammonium carbonate (i), physical mixture with menthol (d), camphor (g), ammonium carbonate (j), tablets after sublimation of menthol (e), camphor (h), ammonium carbonate (k).

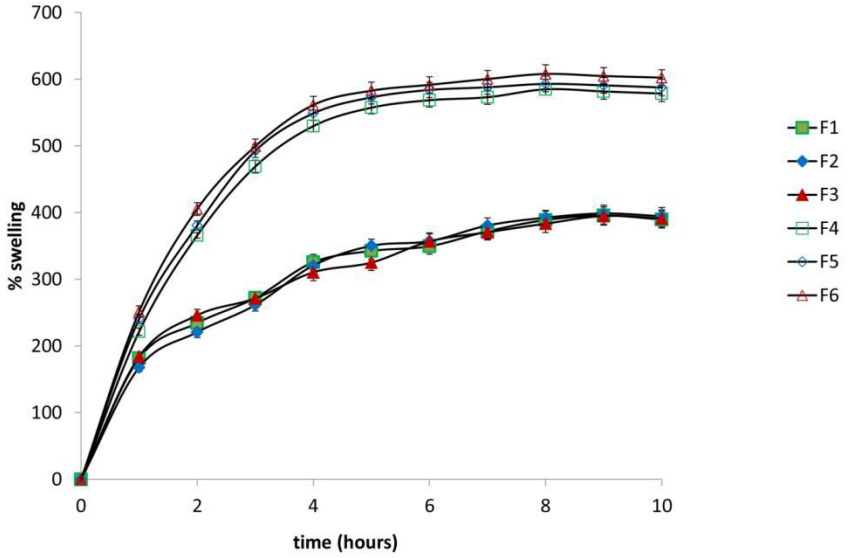

Figure 6: Swelling profiles of HPMC (F1-F3) and PEO (F4-F6) porous tablets.

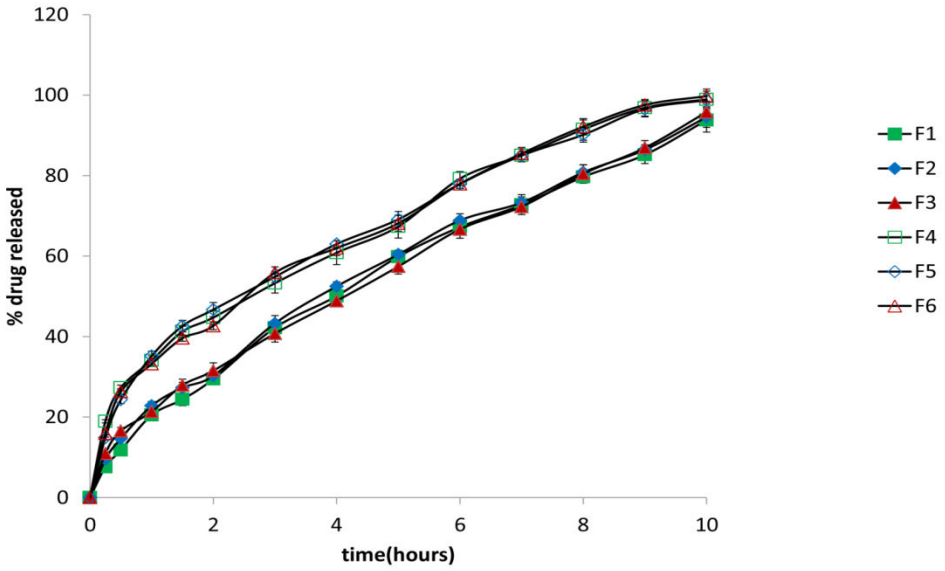

Figure 7: Release profiles of HPMC (F1-F3) and PEO (F4-F6) porous tablets.

References

[1] T. O. h, J. Y. Kim, J. M. Ha, S. C. Chi, Y. S. Rhee, C. W. Park and E. S. Park, *Eur J Pharm Biopharm* 2013, *83*, 460-467.

[2] A. Streubel, J. Siepmann and R. Bodmeier, *Expert Opin Drug Deliv* 2006, *3*, 217-233.

[3] V. D. Prajapati, G. K. Jani, T. A. Khutliwala and B. S. Zala, *J Control Release* 2013, *168*, 151-165.

[4] A. Badoni, A. Ojha, G. Gnanarajan and P. Kothiyal, *The Pharma Innovation* 2012, *1*, 32-40.

[5] Y. Kawashima, T. Niwa, H. Takeuchi, T. Hino and Y. Itoh, *J Pharm Sci* 1992, *81*, 135-140.

[6] A. Streubel, J. Siepmann and R. Bodmeier, *Eur J Pharm Sci* 2003, *18*, 37-45.

[7] R. Talukder and R. Fassihi, *Drug Dev Ind Pharm.* 2004, *30*, 405-412.

[8] M. Fukuda and A. Goto, *Chem Pharm Bull* 2011, *59*, 1221-1226.

[9] R. S. Kesarla, P. A. Vora, B. Sridhar, G. Patel and A. Omri, *Drug Dev Ind Pharm* 2014, 1-13. doi:10.3109/03639045.2014.959969.

[10] G. Pacifici, B. Giulianetti, M. Quilici, R. Spisni, M. Nervi, L. Giuliani and R. Gomeni, *Xenobiotica* 1997, *27*, 279-286.

[11] D. Goldstein, Y. Tan and S. Soldin, *Eur J Clin Pharmacol* 1987, *32*, 631-634.

[12] a) L. Meka, B. Kesavan, K. M. Chinnala, V. Vobalaboina and M. R. Yamsani, *AAPS PharmSciTech* 2008, *9*, 612-619; b) S. Baumgartner, J. Kristl, F. Vrečer, P. Vodopivec and B. Zorko, *Int J of Pharm* 2000, *195*, 125-135.

[13] C. Balazs and S. E. Leucuta, *FARMACIA-BUCURESTI-* 2008, *56*, 244.

[14] J. D. Perez-Ramos, W. P. Findlay, G. Peck and K. R. Morris, *AAPS PharmSciTech* 2005, *6*, E127-136.

[15] A. T. Nouh, E.-G. A. Abd and T. K. Guda, *Drug Discov Ther* 2010, *4*, 85-92.

[16] P. Prasad Verma and A. Chandak, *Acta pharmaceutica* 2009, *59*, 171-186.

[17] M. El-Badry, M. A. Hassan, M. A. Ibrahim and H. Elsaghir, *Farmacia* 2013, *61*, 1137-1150.

[18] J. Djuris, I. Nikolakakis, S. Ibric, Z. Djuric and K. Kachrimanis, *Eur J Pharm Biopharm* 2013, *84*, 228-237.

[19] M. Rajab, M. Jouma, R. H. Neubert and M. Dittgen, *Drug Dev Ind Pharm* 2014, *40*, 879-885.

[20] P. Todd, J. L'Hote-Gaston and M. Sheick, *Poster presented at 2008 annual meeting and exposition of AAPS, Atlanta, Georgia* 2008.

[21] D. Sanjeevani, P. Madhavi, S. Ajinath and S. Satish, *J Pharm Educ Res* 2013, *4*.

[22] J. Siepmann and N. Peppas, *Adv Drug Deliv Rev* 2012, *64*, 163-174.

Corresponding author:

May Saab*,

Email: *saabk.may79@yahoo.com*