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Alternative approaches in formulating floating hollow tablets *via* sublimation technique; a platform tailored drug release profile

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The aim of this study was to formulate floating hollow tablets of salbutamol sulphate with a platform tailored drug release profile to attain a controllable drug release. Eight formulations (F1-F8) were prepared using sublimation technique. L-menthol was directly compressed as sublimable core followed by compression coating of hydroxypropylmethyl cellulose (HPMC-K15M) or polyethylene oxide (PEO-WSR301) as release retarding polymer coat. Tablets were then subjected to heat to allow sublimation of the core. The effect of polymer type and that of different drug coat/core distribution on swelling and drug release profile was studied. FTIR and DSC revealed the absence of any drug-excipients interaction. Tablets showed a hollow morphology, resulting in low density tablets that floated for over 24 hours without lag time. Moreover, different drug coat/core distribution resulted in controllable release profiles. Based on these results, an optimum drug release behavior was recorded for HPMC-based hollow tablets consisting of 2:1 drug coat/core distribution ratio (F4), revealing a zero order drug release for over 14 hours. Furthermore, F4 showed no changes in drug content, floating properties and drug release profile upon exposure to accelerated stability conditions.

1. Introduction

Oral sustained drug delivery systems (OSDDS) have gained much interest in the last decade (Prajapati et al. 2013). Such systems have the advantage of enhancing patient compliance, and improving the drug pharmacokinetics. Despite the growth of OSDDS, they display a limitation for drugs with narrow absorption window (e.g. drugs specifically absorbed from upper part of gastrointestinal tract). This limitation can be attributed to their inability to retain the drug at the absorption site for a sufficient time required for complete absorption. In order to overcome this limitation, gastroretentive (GR) drug delivery systems would be beneficial in increasing the gastric residence time of the drug, and sustaining the release profile at the absorption site (Streubel et al. 2006).

Various techniques for gastric retention have been discussed in the literature, namely high density, magnetic, mucoadhesive, floating and swelling systems (Prajapati et al. 2013). The floating drug delivery systems are considered the most popular among the aforementioned dosage forms. Their low densities enable them to float on the surface of gastric fluids for a predetermined period of time (Badoni et al. 2012).

Several methods have been used to prepare GR floating dosage forms. These include the incorporation of effervescent materials (carbonates or bicarbonates) that react with citric acid or gastric fluid (He et al. 2012; Xu et al. 2006), the use of low density materials such as polypropylene foam powder (Streubel et al. 2003), and the application of ionotropic gelation to produce low-density hollow beads (Badve et al. 2007; Svirskis et al. 2014; Taranalli et al. 2015). The sublimation technique is another approach that was extensively used in the formulation of orodispersible tablets (Badgujar et al. 2011; Fu et al. 2004; Kalyankar et al. 2015), and has been adopted in the last few years for the development of floating drug delivery systems (Fukuda et al. 2011; Kesarla et al. 2015; Kim et al. 2014; Oh et al. 2013). In this technique, hollow or porous low density floating tablets can be produced following the sublimation of sublimable agents such as L-menthol and camphor.

In the present study salbutamol sulphate (SS) was selected as a model drug in the development of GR floating hollow tablets using the sublimation technique. Salbutamol sulphate is a bronchodilator with a short biological half life of 3.8 hours and a site-specific absorption (stomach and upper part of small intestine) (Goldstein et al. 1987). Therefore, SS represents a good candidate for GR floating hollow tablets. Polyethylene oxide (PEO WSR 301) or hydroxypropylmethyl cellulose (HPMC K15M) were used as the tablet polymer coat, and L-menthol as sublimable core.

In previous studies, the use of high polymer content was described as a strategy to get better control over drug release profile (Kesarla et al. 2015; Oh et al. 2013). However, this may have several drawbacks such as, increase in tablet density, thereby affecting floating properties. Moreover, high polymer content may be disadvantageous from an economic point of view.

In this study, relatively low polymer content was employed in formulating GR floating hollow tablets, and the effect of drug coat/core distribution on the drug release behavior was investigated as an alternative approach to control drug release.

2. Investigations and results

2.1. Morphological examination

Before sublimation of menthol, the cross sectional morphology of tablets showed a dense structure consisting of menthol core surrounded by polymer coat (Fig. 1a). After sublimation, the cross sectional morphology revealed a hollow structure, indicating complete sublimation of L-menthol core (Fig. 1b).

2.2. Compatibility studies

2.2.1. Differential Scanning Calorimetry (DSC)

The DSC thermograms of pure SS, L-menthol, polymers (HPMC and PEO), physical mixtures and tablets after sublimation were illustrated in Fig. 2. The spectrum of SS revealed a sharp endothermic peak at 196.78 °C. This may be attributed to the crystalline nature of the drug and its melting. L-Menthol showed an endothermic peak at 44.45 °C indicating its melting point. HPMC revealed a broad endothermic peak at 63 °C that is due to polymer

dehydration (Prasad Verma et al. 2009). In case of PEO, an endothermic peak at 69.68 °C was observed, corresponding to the melting of the crystalline polymer. The DSC analysis of SS/HPMC/menthol physical mixture and their corresponding tablets after sublimation (Fig. 2a) showed no changes in SS peak. However, a decrease in SS peak intensity was detected when compared to that of pure drug. On the other hand, physical mixture of SS/PEO/menthol and their corresponding tablets after sublimation (Fig. 2b) showed complete absence of SS peak.

2.2.2. Fourier transform infrared (FTIR)

Figure 3 illustrates spectra of pure SS, polymers (HPMC and PEO), L-menthol, physical mixtures and tablets after sublimation. Characteristic peaks of SS were observed at 3143.07 cm^{-1}(NH stretching) and 1506.48 & 1467.97 cm^{-1}(C=C stretching in aromatic ring). Additional peaks ranged from 2454.5 to 2779.33 cm^{-1} indicating alkyl groups C-H stretching. All the characteristic bands of SS were revealed in the IR spectra of physical mixtures and that of tablets after sublimation, but with a reduction in peaks intensity.

2.3. Evaluation of physicochemical properties of the tablets

2.3.1. Drug content

The drug content of all tablets was in the range of 96.98±1.55 %, revealing the uniformity of drug distribution among all formulations.

2.3.2. Friability

The percentage friability of all formulations recorded a value of 0.59±0.10 % before sublimation, and a value of 0.61±0.07 % after sublimation, which showed an acceptable value when referred to USP35 specifications.

2.3.3. Hardness

Tablets hardness before sublimation ranged from 60.80 to 66.49 N. After sublimation, the hardness showed a reduction by about 25% (45.16 N to 52.37 N).

2.3.4. Density

Prior to sublimation, all tablets recorded a density ranging from 1.01 to 1.13 g/cm^3 that decreased after sublimation by about 35% and ranged from 0.64 to 0.71 g/cm^3.

2.3.5. In-vitro floating behavior

The resulting tablets obtained after sublimation of menthol had no floating lag time with a floating duration of more than 24 h.

2.3.6. Swelling behavior

The effect of polymer type and different drug coat/core distribution on the swelling behavior of tablets is shown in Fig. 4. Formulations containing PEO (F5-F8) revealed a higher swelling extent (~ 1.5 fold) compared to HPMC formulations (F1-F4).

The influence of various drug coat/core distribution on the swelling behavior from either HPMC or PEO tablets was investigated. The results showed a significant difference ($p<0.05$) in their initial percent swelling at the first hour, with the following order: F1>F4>F3>F2 and F5>F8>F7>F6 for HPMC and PEO, respectively (Fig. 4). The highest initial swelling was observed with tablets having the drug completely distributed in the polymer coat (F1 and F5) and the lowest was recorded for tablets having the drug completely embedded in the core (F2 and F6). No significant difference ($P>0.05$) in the maximum percent swelling was detected for all formulations having the same polymer type (Fig. 4), revealing that varying drug distribution did not affect the maximum swelling extent of the polymer.

2.4. In-vitro release study

The effect of polymer type and different drug coat/core distribution on *in-vitro* release profile is shown in Fig. 5. All formulations showed extended drug release profiles that differed in their duration and release rate depending on the type of polymer and drug coat/core distribution. Faster drug release was shown in PEO formulations, recording a significantly smaller T_{50} values (<0.01) when compared to those of HPMC with the same drug coat/core distribution (Table 1). The relatively faster drug release from PEO formulations can be attributed to its higher swelling capacity (Fig. 4), thus absorbing more water and resulting in a faster drug dissolution and diffusion, compared to HPMC. Moreover, different release patterns were observed by varying the drug coat/core distribution in either HPMC or PEO formulations. The drug release was relatively fast for formulations consisting of the drug completely distributed in the coat, namely, F1 and F5 (Fig. 5 A); a high initial drug release was observed for F1 and F5 (Table 2), followed by a sustained drug release reaching about 99% of the drug released after 10 h and 9 h, respectively. Slower drug release rates were observed in formulations consisting of 1:1 and 2:1 drug coat/core distribution ratio, namely F3, F4, F7 and F8 (Fig. 5 B); embedding a part of SS in the core resulted in a significant ($p<0.01$) reduction in the initial drug release and increase in T_{50} and T_{90} (Table 2). Complete release of SS for formulation F8 was attained after 13 h, whereas, F3, F4 and F7 required about 14 h for complete drug release (Fig. 5B).

The slowest drug release rates were recorded for formulations consisting of the drug completely embedded in the core, namely, F2 and F6 (Fig. 5 C); The drug release profile showed a long lag

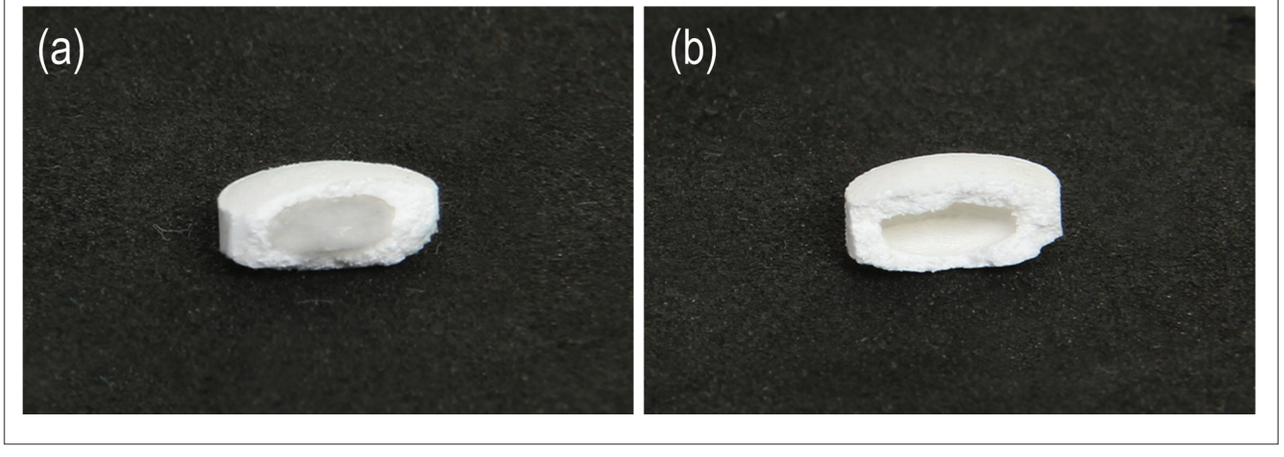

Fig. 1: Cross sectional morphology of SS tablets. (a) before and (b) after sublimation

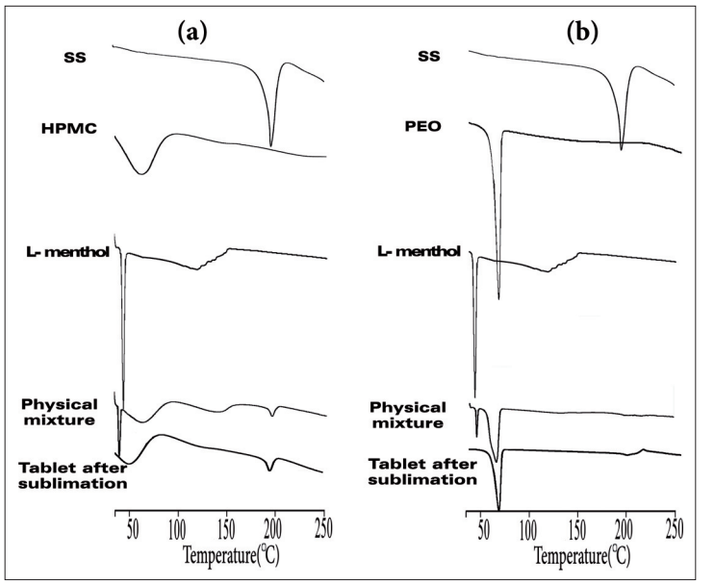

Fig. 2: DSC thermograms of SS, polymer, L-menthol, their physical mixture and corresponding tablets after sublimation, consisting of (a) HPMC or (b) PEO.

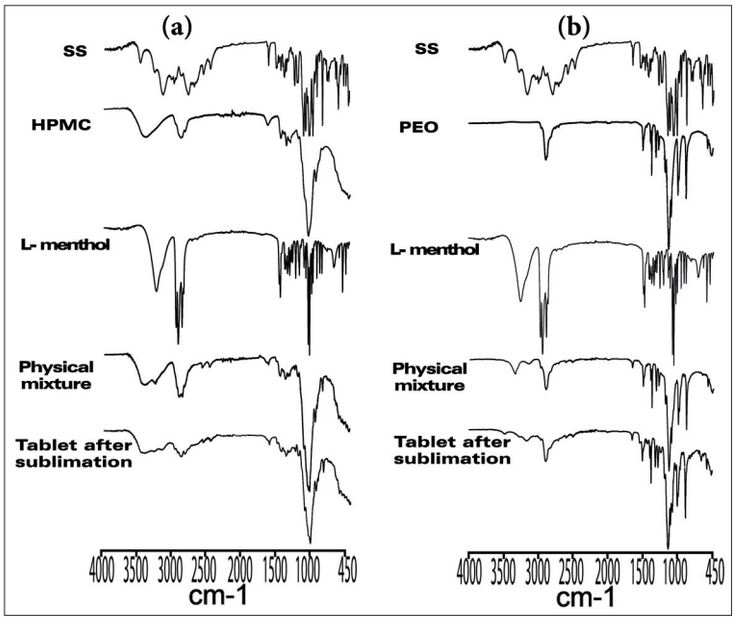

Fig. 3: IR spectra of SS, polymer, L-menthol, their physical mixture and corresponding tablets after sublimation, consisting of (a) HPMC or (b) PEO.

Table 1: Different formulations of SS floating tablets

Ingredient	Formulation code (amount in mg)							
	F1	F2	F3	F4	F5	F6	F7	F8
Salbutamol sulphate in the coat	9.6	-	4.8	6.4	9.6	-	4.8	6.4
Salbutamol sulphate in the core	-	9.6	4.8	3.2	-	9.6	4.8	3.2
HPMC K15M	140.4	140.4	140.4	140.4	-	-	-	-
PEO WSR301	-	-	-	-	140.4	140.4	140.4	140.4
L-menthol	50	50	50	50	50	50	50	50
Total (before sublimation)	200	200	200	200	200	200	200	200
Total (after sublimation)	150	150	150	150	150	150	150	150

Table 2: In-vitro release data of SS hollow tablets (mean ± SD, n=3)

Formulation code	Initial % drug release (at 1 h)	T_{50} (h)	T_{90} (h)
F1	34.86±0.61	2.2±0.15	6.9±0.40
F2*	-	16.2±0.20	23.9±0.25
F3**	-	8.3±0.12	12.6±0.37
F4	9.62±0.62	6.9±0.25	12.7±0.22
F5	38.55±0.96	1.4±0.12	5.8±0.33
F6*	-	14.3±0.22	21.8±0.48
F7	7.77±0.81	7.5±0.30	12.9±0.50
F8	11.59±0.94	6.2±0.28	11.7±0.35

* Initial release of SS after 7 h
** Initial release of SS after 1.5 h

F5<F8<F7<F6, respectively (Table 3), indicating an increase in n value with increasing the level of the drug embedded in the core and decreasing that in the coat.

2.6. Stability studies

Formulation F4 was selected for accelerated stability studies; recording a zero order (n=0.89) controlled drug release for more than 14 h. The results from the accelerated stability study of the selected tablets revealed insignificant differences in their drug content, floating behavior and drug release profiles. Similarity factor analysis for the drug release profile between the freshly prepared and the three months stored tablets recorded a f_2 value above 50 (84.3), confirming the similarity in drug release from both the freshly prepared and stored tablets (Fig. 6).

Table 3: In-vitro release kinetics of the prepared SS tablets

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Hixson-Crowel R^2	Korsmeyer-Peppas R^2	n
F1	0.9167	0.9484	0.9899	0.9843	0.9943	0.47
F2	0.9911	0.8851	0.9867	0.9433	0.9531	2.40
F3	0.9876	0.7017	0.9464	0.8511	0.9808	1.33
F4	0.9982	0.8179	0.9481	0.9276	0.9969	0.89
F5	0.8743	0.9190	0.9846	0.9857	0.9897	0.61
F6	0.9921	0.8747	0.9799	0.9582	0.9992	2.91
F7	0.9960	0.6363	0.9484	0.8516	0.9084	1.35
F8	0.9970	0.7443	0.9718	0.9029	0.9935	0.88

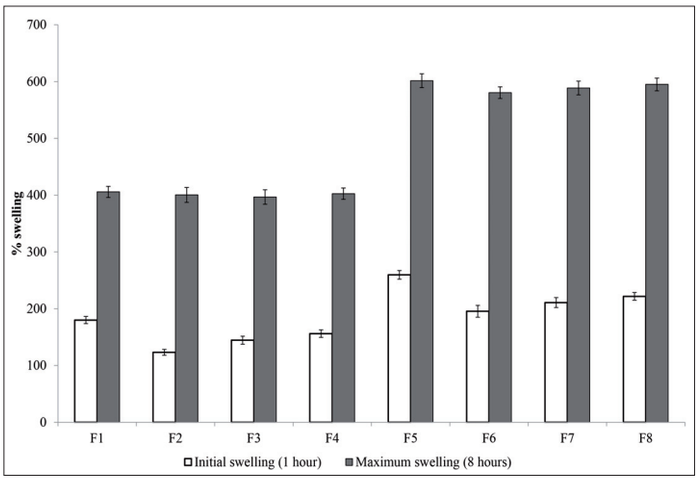

Fig. 4: Swelling profiles of HPMC (F1-F4) and PEO (F5-F8) tablets with different drug coat/core distributions.

period (7 h) before it started to be released in a sustained manner from the tablets for over 24 h, thereby, recording the highest T_{50} and T_{90} values (Table 2).

2.5. In-vitro release kinetics

The results showed that formulations consisting of drug completely distributed in the coat (F1 and F5) were best fitted to Korsmeyer-Peppas equation recording the highest R^2 values among other kinetic models (Table 3). All other formulations consisting of part of drug amount or entire drug amount embedded in the core were best fitted to zero order equation where a more controlled drug release was observed. The n values of both HPMC and PEO formulations had the following order: F1<F4<F3<F2 and

3. Discussion

Formulations of either HPMC or PEO hollow tablets were prepared using L-menthol as a sublimable core. The tablets consisted of different drug coat/core distribution, in an attempt to obtain an optimum formulation, displaying desired floating properties and controlled drug release profile.

The DSC thermograms indicated the compatibility of SS with other excipients; the observed reduction in the peak intensity of SS thermogram in presence of HPMC can be attributed to the diluting effect of the polymer (El-Badry et al. 2013). On the other hand, the complete absence of the drug thermogram in presence of PEO, can be explained by the molecular dispersion of the drug in the molten polymer during the heating process of DSC (Djuris et al. 2013; Ozkan et al. 2000). Furthermore, All HPMC and PEO tablets

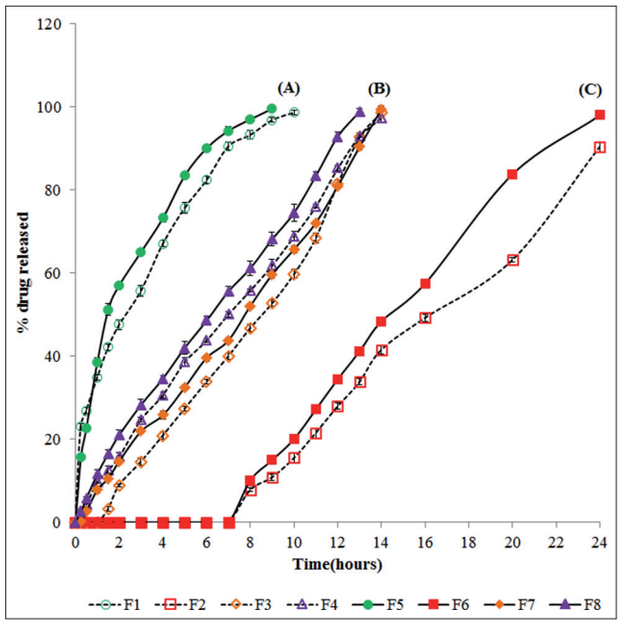

Fig. 5: Release profiles of HPMC (F1-F4) and PEO (F5-F8) tablets with different drug coat/core distribution. (A) drug in coat, (B) drug in coat and core and (C) drug in core.

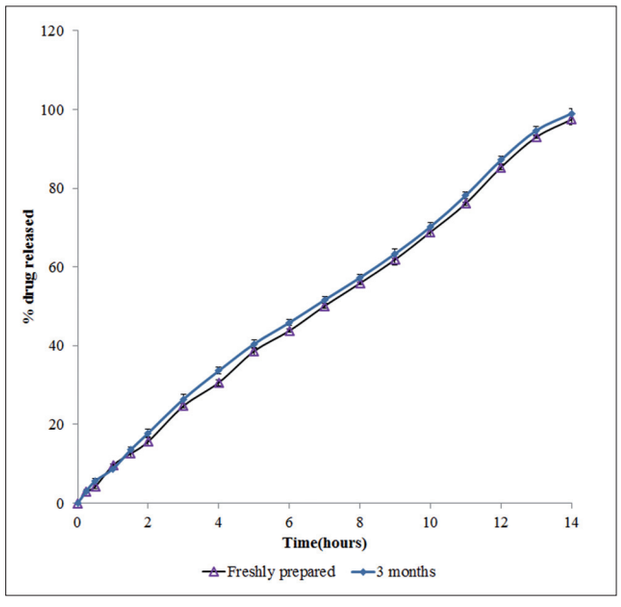

Fig. 6: Effect of accelerated stability storage on the release profile of SS from the selected formulation (F4).

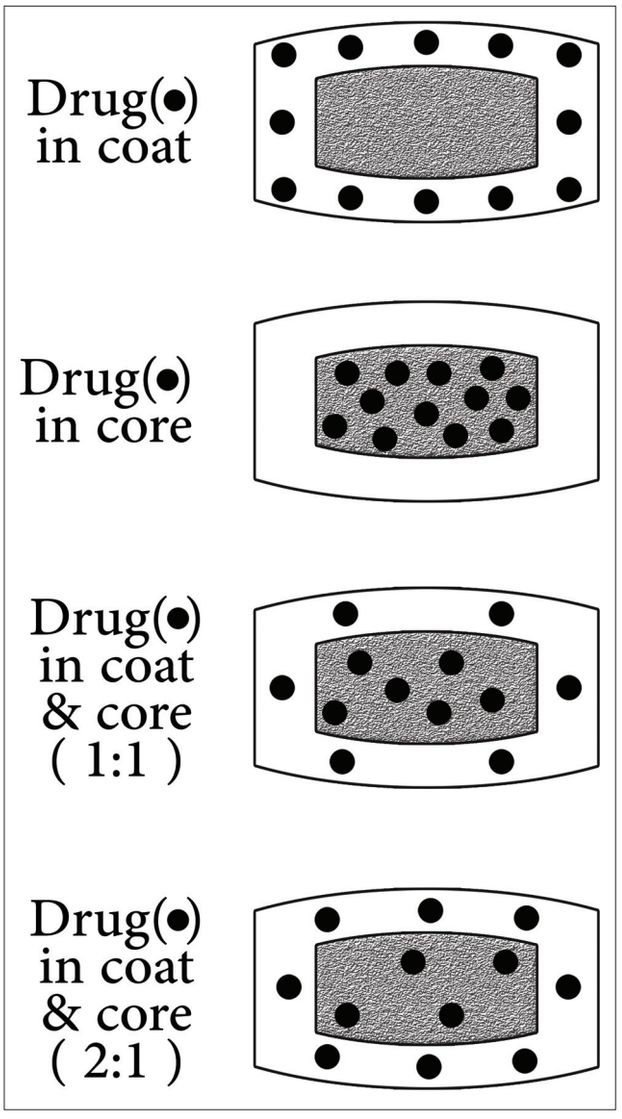

Fig. 7: Schematic presentation of tablets with drug incorporated within L-menthol core, within polymer coat (HPMC or PEO), followed by tablets with different drug coat/core distribution.

revealed the absence of menthol endotherm, confirming its complete sublimation. Similarly, FT-IR spectra indicated no drug-excipient interaction; the decrease in peak intensity of the drug corresponds to its dilution in the mixture as previously reported by Eloy et al. (2014). These results confirm the results obtained by DSC.

All tablets had an acceptable range of drug content reflecting the uniform drug distribution in the mixture. Tablets friability values showed no significant difference before and after sublimation, but a significant decrease in tablet hardness was recorded, that is in accordance with Kesarla et al. (2015). Despite this reduction, the hardness was within acceptable limit as specified by USP35. Such finding can be explained by the hollow morphology of tablets that decreased their mechanical strength (Fig. 1).

The density of tablets was also reduced after sublimation of l-menthol, by creating a hollow structure in the tablet. Fukuda et al. (2011) have previously reported the use of l-menthol as a core in the preparation of famotidine hollow tablets. After sublimation, the tablets were dip-coated in molten waxy polymers. Immediate floating of the resultant hollow tablets was observed, that persisted for over 6 h.

In our study, all tablets floated immediately and remained floating for more than 24 h. The hollow structure of the tablets obtained after sublimation of menthol core played an important role in reducing the density of the tablets (0.64-0.71 g/cm^3). Furthermore, the hollow structure was maintained by the strong polymeric network, resulting in an immediate floating that was maintained for a long period of time (Oh et al. 2013).

Moreover, the inherent floating of tablets can be related to a relatively low polymer content, that may decrease the chance of a premature gastric emptying, which is advantageous compared with Kesarla et al. (2015). The authors investigated the effect of polymer content on the floating properties of porous tablets. At relatively low polymer content, they stated that tablets had floated immediately for more than 24 h. However, the increase in polymer content resulted in a floating lag time (Kesarla et al. 2015).

A significantly higher swelling extent was observed for all PEO formulations (F5-F8), when compared to HPMC containing

tablets (F1-F4) (Fig. 4). 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 (Maggi et al. 2000). This finding is in accordance with that obtained by Nie et al. (2011), who investigated the effect of polymer type on the swelling extent of theophylline extended release tablets. Their results showed a greater hydration for PEO, compared to HPMC.

The effect of various drug coat/core distribution in either HPMC or PEO formulations revealed a decrease in the initial % swelling with increasing the drug distribution in the core. This may be attributed to the osmotic pressure imparted by the highly hydrophilic drug present in the coat that allowed higher influx of water into the tablets and hence more initial swelling. Later on, the tablets reached the same maximum swelling extent after 8 h. The physical properties of the polymer play a vital role on its transition from its initial glassy to rubbery phase and subsequently on its swelling behavior (Li et al. 2008). However, the interval that is required for the transition is also correlated to the hydrophilicity of the drug (Li et al. 2008). SS being highly hydrophilic, it attracted water and contributed to the fast swelling of the polymer.

The study of drug release from tablets showed that all PEO formulations recorded significantly lower T_{50} values ($p<0.01$) when compared to those of HPMC consisting of similar drug coat/core distribution (Table 2). The relatively faster drug release from PEO can be attributed to its higher swelling capacity as shown in Fig. 4. Furthermore, PEO tablets were previously described to be more susceptible to erosion processes than HPMC tablets, thus contributing to faster drug release. These findings are in agreement with Maggi et al. (2000) who studied the release of diltiazem HCl from PEO and HPMC matrices. The release of diltiazem HCl from PEO matrices was more rapid than its release from HPMC.

Different drug coat/core distribution had a pronounced effect on the drug release profile (Fig. 5). F1 and F5 formulations revealed high initial drug release that was followed by sustained release profile of drug (Fig. 5 A); the drug being concentrated in the polymer coat, a rapid drug diffusion predominated in the initial period. However, the fast swelling process increased tablet dimensions, leading to an increase in diffusional path length and a gradual decrease in drug release (Miranda et al. 2006). In an earlier study conducted by Chavanpatil et al. (2005), ofloxacin effervescent floating tablets were developed and the effect of polymer content on drug release profile was investigated. High initial drug release was observed with a relatively low polymer content that gradually decreased with increasing polymer content in the tablets. In the present study, various drug coat/core distribution were employed as an alternative approach to reduce the initial drug release and achieve better control over drug release profile. The significant reduction ($P<0.01$) in the initial drug release and release rate of F3, F4, F7 and F8 formulations, compared to F1 and F5 (Table 2), can be attributed to the decrease in drug amount in the coat. In addition, a decrease in the initial swelling of the aforementioned formulations when compared to F1 and F5 (Fig. 4) may have contributed to the reduction of initial drug release. These findings are in line with those obtained by Balazs et al. (2008).

When the drug was completely embedded in the core (F2 and F6), tablets revealed a long lag time (7 h), before releasing the drug in a sustained manner for more than 24 h. This finding is attributed to the swelling of the polymer when in contact with the dissolution medium without any drug release. Once water reached the coat, it started to dissolve the drug that diffused slowly through the swollen polymer. Thereafter, the polymer chains increasingly relax, disentangle and erode. In the late stage, the erosion process enhanced to some extent the drug release from the tablet as it compensated to the slow drug diffusion from the swollen polymer (Nagarwal et al. 2010). Although a sustained drug release was obtained, the release lag time may delay the onset of action of SS. However, such drug release pattern could be advantageous in chronotherapy and requires extensive investigations in the future.

The study of the in-vitro release kinetics revealed that the best fitting model for F1 and F5 is that of Korsmeyer-Peppas, and n values were 0.47 and 0.61, respectively, indicating an anomalous drug transport (Table 3). These results are in accordance with Sanjeevani et al. (2013), where drug release is mainly governed by both drug diffusion through the swollen polymer and erosion of the latter. All other formulations are best fitted to zero order model. The presence of the entire drug amount or part of it embedded in the coat resulted in a more controlled drug release when compared to F1 and F5 (Fig. 5). Many efforts were exerted by researchers in attaining zero order controlled drug release matrices, however, few have succeeded (Jamzad et al. 2006; Mostafavi et al. 2011). In this study, HPMC and PEO Formulations (F4 and F8) consisting of 2:1 drug coat/core distribution ratio recorded n values of 0.89 and 0.88, respectively, thereby indicating a case II erosion-controlled process. The increase in n value above 0.89 (F2, F3, F5 and F7) indicated that the release mechanism shifted from case II to super case II, in which drug release in the latter stages is highly dependent on a rapid relaxation-controlled process (Meka et al. 2008; Shah et al. 1998). Among all aforementioned formulations, F4 and F8 showed the best drug release behavior, where n values literally reflect the best fit for zero order release kinetic model, indicating a constant drug release rate. However, F4 was chosen as the optimum formulation, providing a controlled drug release for over 14 h compared to 13 h in F8, and was stable under accelerated stability conditions by recording no changes in drug content, floating properties and drug release profile.

All formulated hollow tablets displayed an immediate floating that persisted for more than 24 h. The polymer type and different drug coat/core distribution, proved to have a pronounced effect on the swelling and drug release behavior of the hollow tablets. Tablet formulation (F4) consisting of HPMC polymer and 2:1 drug coat/core distribution ratio was chosen as the optimum formulation. It showed a relatively low initial drug release in the first hour (9.63%) and a zero order controlled release for over 14 h. However, tablet formulations (F2 and F6) consisting of the drug completely embedded in the core showed a release behavior (release lag time of 7 h) that could be advantageous for chronotherapy. From the results obtained, it can be concluded that hollow tablets showed to be a promising gastroretentive drug delivery system, providing excellent floating properties and "tailoring" the drug release by changing the drug coat/core distribution. Further studies should be conducted by applying this approach on other drugs and polymers and investigate its ability to provide drug delivery systems with different release behaviors that can be implicated for different purposes.

4. Experimental

4.1. Materials

Salbutamol sulphate (SS) was a gift from Mediphar laboratories, Beirut, Lebanon. L-menthol as well as Polyethylene oxide (PEO WSR 301) were purchased from Sigma Aldrisch, USA. Hydroxypropylmethyl cellulose (HPMC K15M) was purchased from Alexandria Pharmaceutical Co., Alexandria, Egypt. All other ingredients were of analytical grade (Fluka, Germany).

4.2. Preparation of GR floating hollow tablets

Eight formulations were prepared by the compression coating method (Table 1). l-Menthol was compressed as the core using a single punch tablet press (Vanguard Pharmaceutical Machinery, Inc. USA) equipped with a 6 mm double concave punch. Subsequently, the core was manually placed within the polymer powder (HPMC K15M or PEO WSR 301) prior to compression coating using 9 mm double concave punch. Drug coat/core distribution varied from one formulation to another (Fig. 7). Tablet hardness was adjusted between 60.80 N and 66.49 N.

All tablets were subjected to heat in hot air oven (Gallenkamp, England). HPMC based tablets were subjected to hot air oven at 80 °C for 3 h period to allow complete sublimation of L-menthol. However, PEO based tablets needed more time (12 h) at low temperature of 50 °C, to permit sublimation of menthol without melting of the polymer (Saab et al. 2015). The weight of each tablet was regularly measured, till obtaining constant weight indicating complete sublimation of L-menthol.

4.3. Morphological examination

Cross sections of tablets before and after sublimation were compared visually to detect morphological changes using digital camera (Canon, EOS 760D, 24.2 Mpixel, Japan)

4.4. Compatibility studies

4.4.1. Differential scanning calorimetry (DSC)

Pure drug, polymers, L-menthol, physical mixtures and tablets after sublimation, were analyzed using Shimadzu differential scanning calorimeter (DSC-60, Japan). Samples of each powder 3 mg were heated at a rate of 5 °C/min in the range of 30–250 °C under nitrogen atmosphere (flow rate 20 mL/min).

4.4.2. Fourier transform infrared (FTIR)

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

4.5. Evaluation of physicochemical properties of the formulated tablets

4.5.1. Drug content

Tablets were assayed for their content uniformity. Samples equivalent to 9.6 mg of SS were dissolved in 100 ml 0.1 N HCl and analyzed spectrophotometrically using Jasco spectrophotometer (V-530, Japan) at λmax 276 nm.

4.5.2. Friability

Tablets friability was determined using Erweka Friabilator (TADR-61823, Germany) according to the following equation:

$$\%\text{friability} = \frac{Wi - Wf}{Wi} \times 100$$

where Wi is the initial weight of the tablets and Wf is their final weight.

4.5.3. Hardness

Hardness (N) of tablets was measured (average of six measurements for each formulation) using Erweka hardness tester (MT-62256, Germany).

4.5.4. Density

Tablets density was calculated as the weight of tablet (W) in g/volume of biconvex tablet (V) in cm^3. The volume of the tablet was derived from the following equation (Perez-Ramos et al. 2005):

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

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

4.5.6. In vitro floating behavior

Floating behavior of each formulation was monitored using Nessler tube (100 ml) having 0.1 N HCl (Oh et al. 2013).

4.5.7. Swelling behavior

Tablets were studied for their swelling behavior in 0.1N HCl (500 ml) at 37 °C±0.5°C using USP dissolution apparatus II (Jacso, Japan) with rotating paddle adjusted at 50 rpm. The tablets were removed regularly (one hour interval) and weighed after blotting excess water. The percentage swelling was calculated as follows:

$$\text{Swelling (\%)} = \frac{Ws - Wo}{Wo} \times 100$$

where Ws (mg) is the weight of the swelling tablet (mg) and Wo (mg) is its original weight. All the results obtained were the average of three determinations.

4.6. In-vitro release study

The release profile of SS from all formulations was performed using USP dissolution apparatus II, containing 500 ml of 0.1 N HCl , kept at 37±0.5 °C and rotated at 50 rpm (Yilma et al. 2015). At predetermined time intervals, samples (5 ml), were withdrawn, filtered through a millipore filter (0.45 µm) and spectrophotmetrically assayed at 276 nm.

4.7. In-vitro release kinetics:

Different release kinetic models were investigated through fitting the release data in such models, namely Higuchi, Hixson–Crowell, Zero-order, First-order, and Korsmeyer–Peppas equations (Costa et al. 2001). The selection of the appropriate model was based on choosing the best fit, where the coefficient of determination value (R^2) approximates 1. To explain the mechanism of drug release, dissolution data for the first 60% drug release were fitted to the Korsmeyer-Peppas model and the release exponent (n) was determined (Bettini et al. 2001). When n value is equal to 0.45, it indicates a case I transport mechanism (Fickian diffusion). If n ranges between 0.45 and 0.89, it correponds to a an anomalous transport mechanism (non-Fickian), and when it attains 0.89, it indicates case-II tranport (zero-order) (Siepmann et al. 2012). If n exceeds 0.89, this means displaying a super case-II transport mechanism (Vueba et al. 2004).

4.8. Stability studies

To assess the stability of the optimum formula, accelerated stability studies were performed according to WHO and ICH guidelines (Matthews 1999). Tablets were packed in aluminium foil at 40°C/75% relative humidity for a period of 3 months (Patil et al. 2013; Thumma et al. 2009; Trivedi et al. 2011). Samples were removed at different intervals and evaluated for drug content, floating behavior and drug release. The release profile of SS from the freshly prepared tablets was compared with that of the three months stored tablets using the similarity factor (f_2); a measurement of the similarity in the percent drug release between the two profiles. In general, f_2 value should be between 50 and 100, indicating an average difference of not more than 10 % in drug release (Shah et al. 1998). The similarity factor is calculated as follows:

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum |Rt - Tt|^2\right]^{-0.5} \times 100\right\}$$

where n is the number of time intervals, Rt and Tt are the percentage drug release of the reference freshly prepared and the tested three months stored tablets, respectively, at time t.

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