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STUDY OF FREE-FILMS AND COATED TABLETS BASED ON HPMC AND MICROCRYSTALLINE CELLULOSE, AIMED FOR IMPROVE STABILITY OF MOISTURE-SENSITIVE DRUGS

Abbaspour MR[1,2*], Sharif Makhmalzadeh B[1,2], Jalali S[2]

[1]*Nanotechnology Research Centre, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*

[2]*Department of Pharmaceutics, School of pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*

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Abstract

Hydrolysis is the dominant process in degradation of drugs, especially for esteric compounds e.g. aspirin. There are several methods for moisture protection of drugs including reduction of drug solubility, modification of chemical structure, moisture-resistant packaging and coating of solid dosage forms. Specific polymer coatings are used to protect moisture sensitive drugs. The aim of this study is to design and evaluate a moisture-resistant film formulation based on HPMC and microcrystalline cellulose (Avicel) and its comparison with Sepifilm® as a commercial gastro- soluble composition for the film coating of moisture sensitive solid dosage forms. Free films of HPMC containing different amounts of Avicel (10, 20, 30 and 40% w/w) and 5% w/w stearic acid as plasticizer were prepared by casting-solvent evaporation method. Free films were then evaluated for their mechanical strength (tensile test), moisture permeability (water vapor transmission test) and morphological properties (SEM). The optimum film formulation was selected to apply as a film coating on tablets containing aspirin (as a moisture sensitive model drug) by fluidized-bed coating. Coated tablets were stored at 40ºC and 75% RH for 2 months. In order to evaluate stability; drug release rate, disintegration time, hardness, and amount of remained aspirin, tablets were studied after 30 and 60 days. The results showed that addition of stearic acid led to improvement of mechanical properties and increase elongation of free films. By increasing amount of Avicel, the water transition rate of free films decreased. HPMC films containing 30% Avicel and 5% stearic acid showed closer properties to Sepifilm® and could be applied as a moisture-resistant film coating and provide acceptable stability for aspirin tablets. These tablets showed the same characteristics as Sepifilm® coated tablets.

Keywords:

Film coating, moisture-resistant, stability, Sepifilm®

Introduction

Water is one of the most commonly involved factors in drug degradation process. Moisture barrier coatings are conventional polymer coatings currently promoted for application to oral solid`dosage forms to minimize the sorption of environmental water vapor and prevent hydrolytic drug degradation. Moisture barrier coatings should have low permeability (1). In order to achieve rapid disintegration of coated dosage forms *in vivo*, it is essential that moisture barrier coatings be water soluble. As far as it has been known, there is no single water

*Email: abbaspourmr@ajums.ac.ir

soluble polymer that is also a good water vapor barrier (2). The approach commonly used in developing pharmaceutical moisture barrier coatings is usually a compromise between the needs for moisture barrier functionality and liquid water solubility. This is usually attained by fabricating systems that combine elements of hydrophilicity (use of a water soluble polymer as the film former) and hydrophobicity (incorporation of materials with moisture repellent or scavenging properties) (2). It is well known that polymeric materials deteriorate considerably on contact with water. This can be a problem to the concept of moisture barrier coatings, since contact with moisture will significantly affect barrier performance. Water is an effective plasticizer, and in particular, affects polymeric materials by decreasing their glass transition temperature which facilitates chain motion. As a result, residual water decreases the mechanical properties (3,4) and adhesive strength of polymer systems (5,6), and in some cases, may lead to production of cracks or leaching of soluble components like plasticizers and wetting agents (7,8). Sepifilm® is a commercial gastrosoluble compound for the film coating of moisture sensitive solid particles that mainly composed of HPMC as a film forming agent, microcrystalline cellulose as binder and stearic acid as a hydrophobic plastisizer (9). It could readily dispersed in water and be used for coating of solid dosage forms. Microcrystalline cellulose (Avicel) had been shown to be as a molecular sponge in contact with water (10), so it is expected to act as a moisture scavenger in coating formulations. Aspirin as a moisture sensitive model drug is a substituted phenyl ester, which is hydrolyzed to salicylic acid and acetic acid on exposure to moisture (11).

The aim of this study is to prepare a moisture-resistant film formulation based on HPMC and microcrystalline cellulose and evaluation of its capability to protect the aspirin tablets from chemical or physical instabilities compare to Sepifilm® as a commercial gastro-soluble composition for the film coating of moisture sensitive solid dosage forms.

Materials and methods

Aspirin was a gift from Hakim Pharmaceutical Co.(Iran), HPMC K100 was supplied by Colorcon (UK), Sepifilm® was provided by Seppic (France), Avicel was a gift from Akbarieh Co. (Iran), spray-dried lactose was provided by Abureyhan Co. (Iran), stearic acid, sodium acetate trihydrate and glacial acetic acid were supplied by Merck (Germany). All materials were used as received unless otherwise specified.

Preparation of free-films

Free-films were prepared by casting-solvent evaporation method. The composition of film formulations are shown in table 1. HPMC or Sepifilm® were added to distilled water and stirred by a mechanical stirrer for about 1 h to achieve a homogeneous dispersion. For addition of stearic acid, the solution was heated to 60 °C, different amounts of Avicel passed through a mesh 200 sieve were added and stirred to reach a homogenous dispersion. The solution was put in refrigerator for 24 h to attain bubble-free solution. 30 mL of dispersion was then poured into glass Petri dishes, and placed in an oven at 50 °C for 24 h. the films were transferred to a desiccator with 100% relative humidity (RH), resulted by water, at room temperature for 10 h, to make the films flexible enough to be removed intact from the plate. The softened films were then cut carefully with a sharp scalpel into several strips of 10 mm width and at least 50 mm length and then peeled off from the plate.

Free films were stored in a desiccator with 50% RH resulted from a saturated solution

of magnesium nitrate hexahydrate at room temperature until mechanical tests were performed.

Water vapor transmission

Water vapor permeation of free films was determined gravimetrically in triplicate. The permeability cups were 3.5 cm in diameter. The inside of the cup was filled with 10 ml of distilled water (100% RH). A circular piece of free films was placed on the cup and a gasket placed on the film followed by a metal ring. The film was held in place with the help of three screw clamps. Another circular piece of the same free film fixed on another cup without water as a reference. Both samples and reference were accurately weighed (±0.0001 g) and then placed in a desiccator containing calcium chloride as a desiccant and filled with silica gel (0% RH). At specific intervals (24, 48, 72, 96 and 120 h), the cups were weighed (±0.0001 g) and the profile of mass change was plotted versus time for each free film. Water vapor transmission (WVT) was calculated using following equation:

$$WVT = \frac{wx}{tAP0(RH1-RH2)}$$

where w/t is the mass change (flux, g/h) resulted from slope of profile of the mass change versus time, x is the film thickness (mm), A, the area of the film surface exposed to the permeant (m^2), P_0 is the vapor pressure of pure water (kPa), and ($RH_1 - RH_2$) is the relative humidity gradient at 25 °C, P_0 is 3.159 kPa (12).

Mechanical test

The thickness of the film strips was measured at five different points using a micrometer and the mean thickness was calculated. Specimens with an average thickness of 100–200 μm were selected. Films with air bubble, nicks or tears and having mean thickness variations of greater than 5% were excluded from analysis. Each specimen was placed between two grips of a material testing machine (REP, China) fitted with a 5 kN load cell. The initial distance between two grips (initial length of the film specimens) was 30 mm and the speed of grip separation was set at 10 mm/min. The % elongation (or % strain at break) were obtained with a computer system attached to the apparatus. The experiment was repeated 5 times for each formulation and the mean value was reported.

SEM

The morphology of the surface of free films and coated tablets was characterized using SEM. The samples were mounted on Al stub, sputter-coated with a thin layer of silver using sputter coater (Polaron, England) under Argon atmosphere, and then examined using SEM (LEO1450VP, England).

Table 1. The composition of different film formulations

Formulation	HPMC(%w/v)*	Avicel(%w/w)**	Stearic acid (%w/w)**	Sepifilm(%)
HPMC	3	-	-	-
HS	3	-	5	-
SA10	3	10	5	-
HSA20	3	20	5	-
HSA30	3	30	5	-
HSA40	3	40	5	-
Sepifilm	-	-	-	3

*Based on water volume

**Based on polymer weight

Tablet coating
Tablets prepared with 40 mg aspirin and 40mg lactose using single punch tabletting machine were coated with HPMC, Sepifilm® and HAS30 coating formulations. The coating was performed using a fluidized bed coater (top spray insert, Werner Glatt, Germany) fitted with a 1 mm nozzle. The inlet air temperature was set at 70 °C and the outlet temperature was in the range of 45–55 °C. The atomizing pressure was 2.0 bar and the spray rate was 5 g/min. The tablets were spray coated until a weight gain of 2% w/w. Coating dispersion was stirred during coating process. The resulted coated tablets were kept in tightly close containers until use.

Dissolution test
Dissolution test was done on 6 tablets in 1000mL of 0.05M acetate buffer (pH 4.50±0.05), using USP apparatus I (basket) at 50 rpm. The samples were taken from the vessels at 5, 10, 15, 30, 60, 90, 120 and 150 minutes and their absorbance was determined by UV spectrophotometer at 279.5 nm.

Stability tests
A modified accelerated stability tests were performed on samples for comparison of capability of different film
formulations to protect the aspirin tablets from chemical or physical instabilities. Different coated tablets were stored at 40 °C and 75% RH for 60 days and evaluated after 30 and 60 days (13). Samples were collected at specified time intervals examined for disintegration time, hardness and remained aspirin contents in tablets (14).

Hardness test
Tablet hardness was determined from the force required to fracture tablets by diametrical compression using a tablet
hardness Tester (Dr. Schleunger 5Y, USA). Mean hardness of 6 tablets from each formulation was reported as tablet hardness.

Disintegration test
The disintegration time was tested on 6 tablets according to the British Pharmacopoeia using a disintegration apparatus (Erweka ZT3, Germany) with discs. Thousand milliliters distilled water was used as disintegration medium and the temperature was set at 37 °C. The time taken until no material from any of the tablets was left on the mesh was recorded.

Determination of remained aspirin
A tablet was milled by mortar and pestle and dissolved in 250 mL water. After filtration of the solution by paper filter, the amount of aspirin in tablets was determined using UV spectrophotometer at 279.5 nm.

Statistical analysis
One-way analysis of variance was used to assess the significance of the differences among various formulations. Tukey-Kramer multiple comparison test was used to compare the means of different groups. Results with $P < 0.05$ were considered to be statistically significant.

Results and discussion
In this study appropriate free films were made and easily peeled off using glass substrate. Free- films made of HPMC and HS formulation were transparent, but free films of HSA10, HSA20, HSA30, HSA40 and Sepifilm® were opaque and white, the reason was the presence of insoluble microcrystallites of Avicel in their formulation. The results of WVT test showed a high water vapor permeation through HPMC films while formulation containing stearic acid and more than 30% Avicel (HSA30 and HSA40) showed significant reduction in WVT compared to HPMC free films ($p<0.05$), WVT of these two formulations also had no significant

differences with Sepifilm® (Fig. 1). Except HPMC free-films, other film formulations have stearic acid as a hydrophobic plasticizer, so the reduction in WVT could be attributed to the presence of hydrophobic component in the formulations. Figure 1 also shows a little decrease in WVT with increase in Avicel content of free-films which was not statistically considerable in the case of HSA10 and HSA20. Average amount of WVT for HSA30 formulation showed closest result to Sepifilm®.

Results of tensile test on free films were in accordance with the results of WVT tests, it means that HMPC free films had the least elongation among different formulations ($p<0.001$) (Fig. 2).

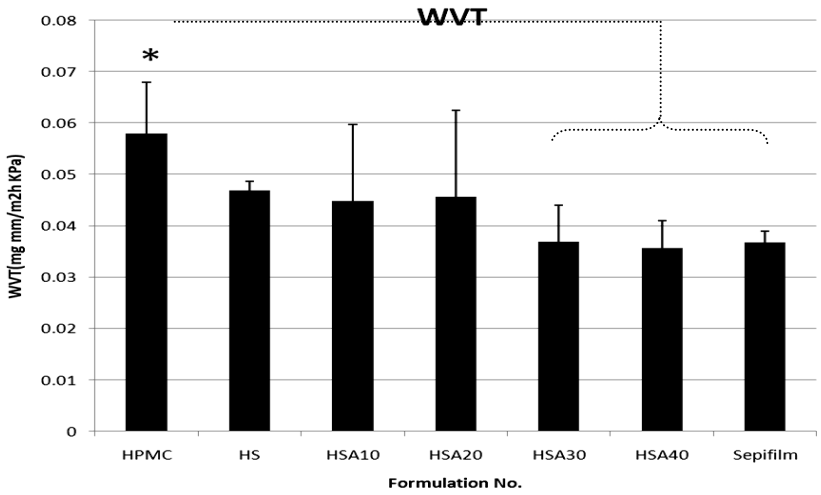


Fig. 1: Results of WVT test on different free films (*$p<0.05$)

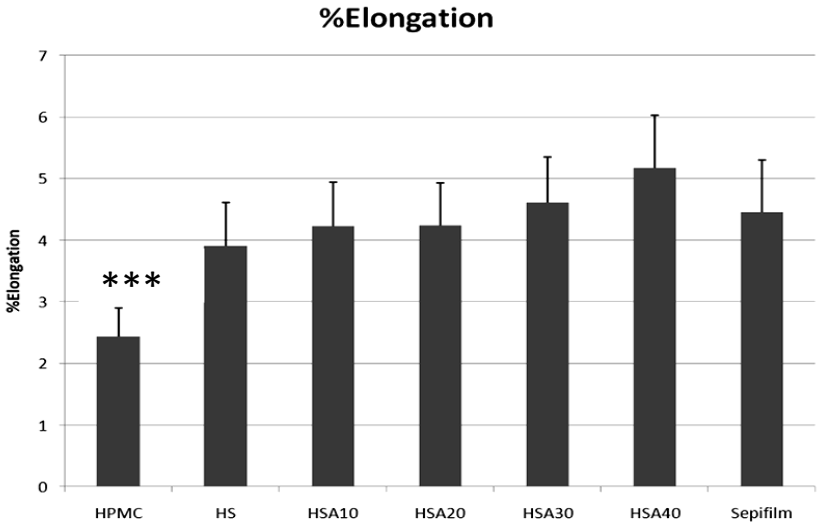
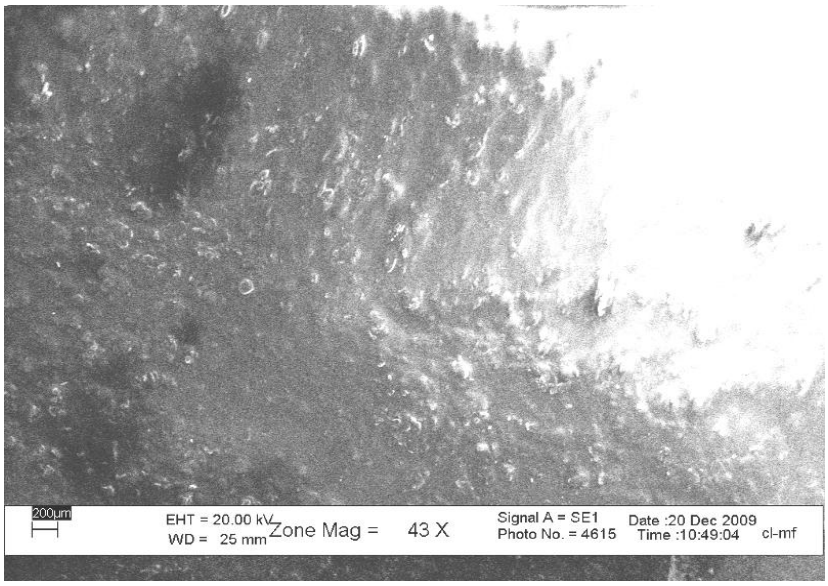
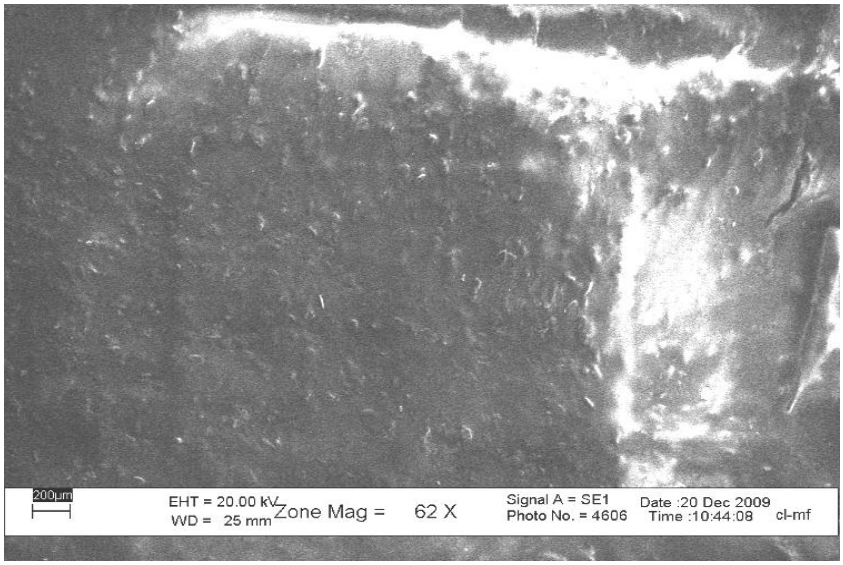


Fig. 2: Results of tensile test on different free films (***$p<0.001$)

Increasing % elongation of films compared with HPMC could be due to the presence of stearic acid as a plasticizer in the formulations. Figure 2 also shows a little decrease in % elongation with increase in Avicel content of free-films, the elongation values of HSA40 was significantly higher than HS, HSA10, HSA20 ($p<0.001$) ,HSA30 ($p<0.05$) and Sepifilm ($p<0.01$). Average amount of % elongation for HSA30 formulation showed nearest result to Sepifilm®. According to these findings, HSA30 formulation was selected for coating of aspirin tablets and their comparison with Sepifilm® or HPMC coated tablets.



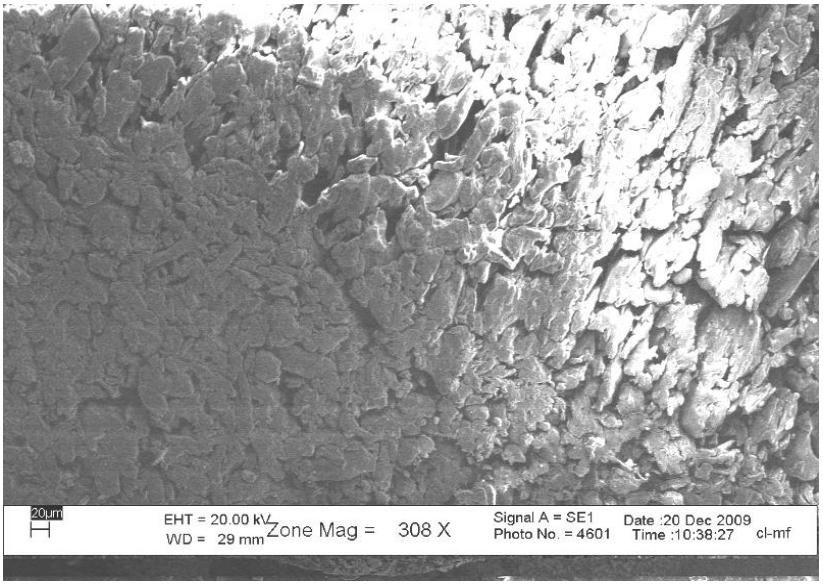
a



b

Fig. 3: SEM images of studied free-films; a: HSA30, b: Sepifilm.

As seen in figure 3, SEM images of HSA30 and Sepifilm® show a uniform distribution of microcrystalline cellulose in their structure that was morphologically similar. SEM images of the surface of coated tablets also show coating integrity and proper coating process (Fig.4).



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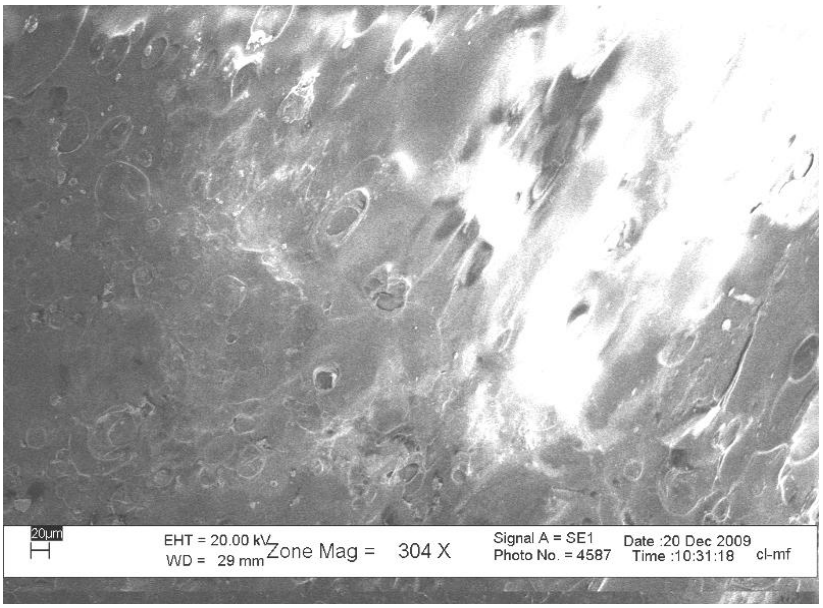

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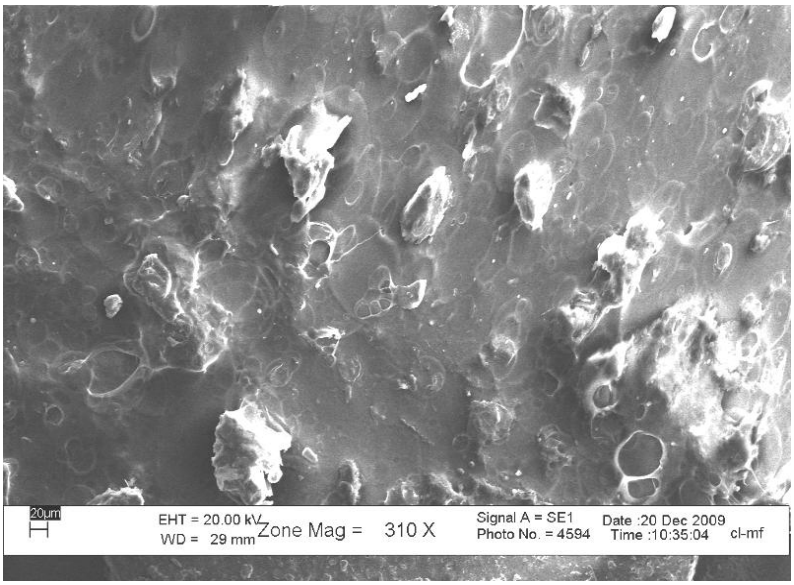

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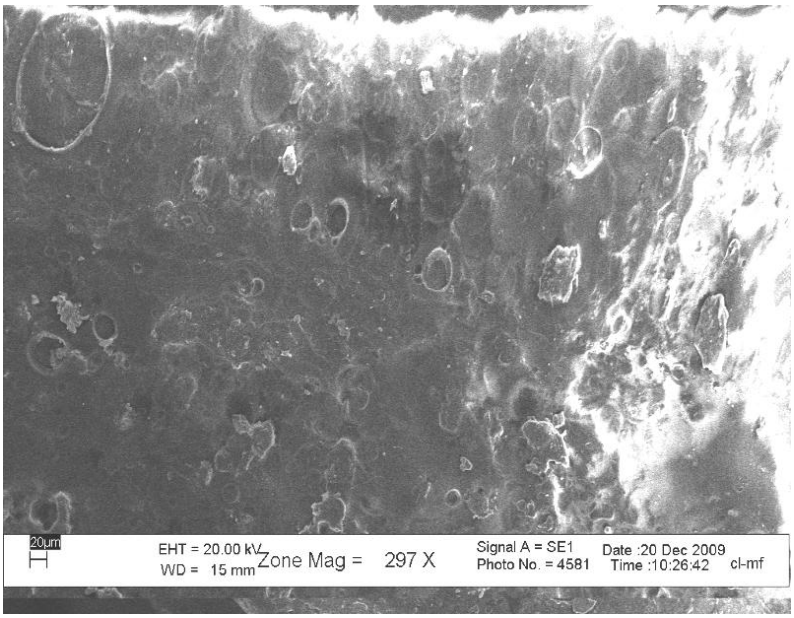

d

Fig. 4: SEM images of surface of studied coated tablets; a: uncoated, b: HPMC, c: HSA30, d: Sepifilm.

Release profile of different coated tablets showed approximately similar drug release with a constant speed and a lag time about 12-15 min in the three formulations (Fig. 5). The lag time in the case of these formulations could be related to the time needed for absorption of water and swelling of HPMC films. Results of tablet hardness tests is shown in figure 6, the results revealed that tablet hardness after one and two months at 40°C and 75% RH was increased, the hardness of coated tablets with HSA30 and Sepifilm® was higher than HPMC coated tablets (Fig. 6). It may be related to binding effect of Avicel which could increase the mechanical strength of coating and increase the total strength of coated tablets with HSA30 and Sepifilm®.

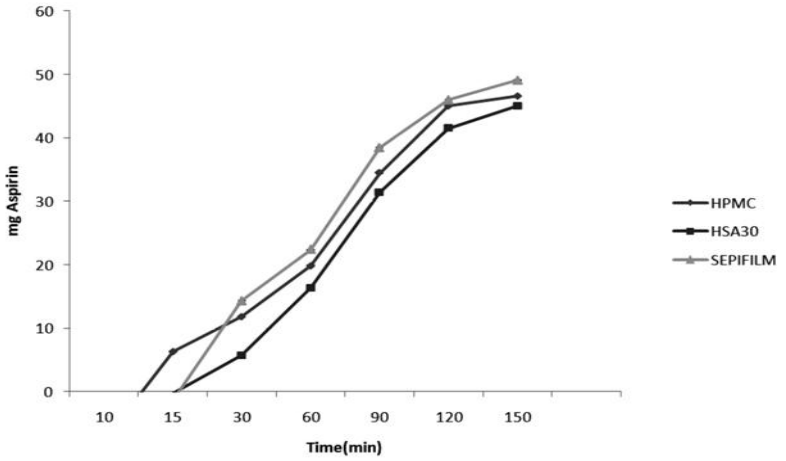

Fig. 5: Release profile of aspirin from different coated tablets.

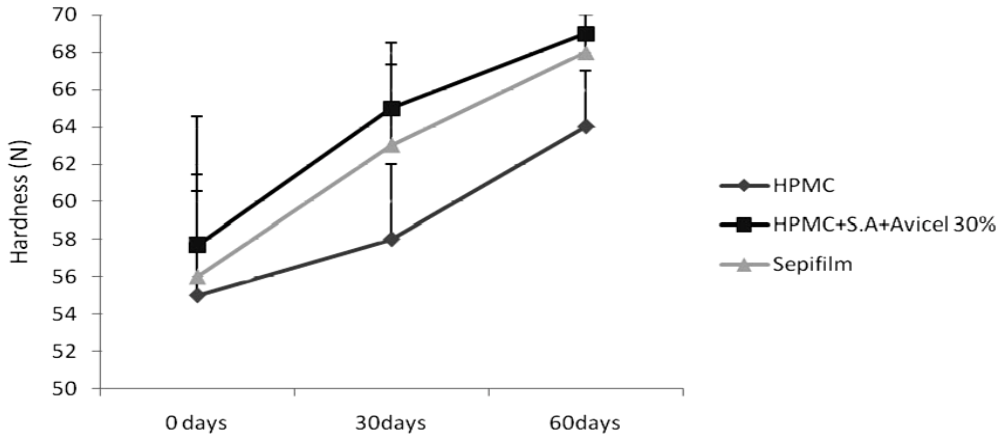

Fig. 6: Changes in tablet hardness after 30 and 60 days at 40°C and 75% RH (*p<0.05)

Figure 7 shows an increase in tablet disintegration time after one and two months at 40°C and 75% RH, but disintegration time of HPMC coated tablets was more than HSA30 and Sepifilm® coated tablets. The reason probably is the presence of Avicel in the coating that increases water intake by the coating and tablets and accelerates disintegration of tablets.

In present study, we have only used 40°C and 75% RH to compare the efficiency of different coating formulations to reduce the rate of drug hydrolysis and improve stability, however, further studies at several elevated temperatures are required to determine the shelf-life of drug at room temperature in order to assess of drug stability of different formulations.

The results obtained by determination of un-hydrolysed aspirin in tablets with HPMC coatings showed a reduction in amount of aspirin remained in tablets after one and two months, while these reduction could be stopped by HSA30 and Sepifilm® coatings after one month (Fig.8).

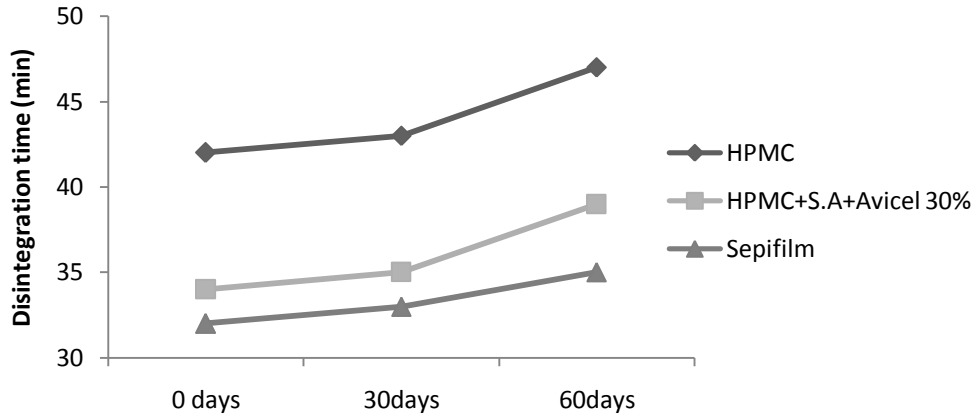

Fig. 7: Changes in tablet disintegration time after 30 and 60 days at 40°C and 75% RH

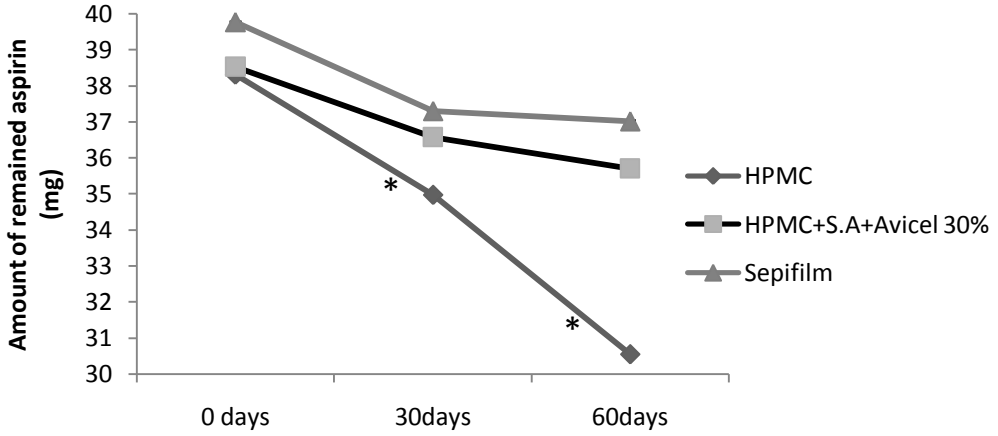

Figure 8. Changes in aspirin content of tablets after 30 and 60 days at 40°C and 75% RH (*p<0.05)

Overall, results show that application of stearic acid and increasing amount of Avicel could improve the moisture resistance and mechanical properties of HPMC free films up to 40 % of Avicel, HAS40 had acceptable WVT but showed lower mechanical strength compared to Sepifilm®, but HAS30 had the most resemblance to Sepifilm®.

Mwesigwa et al. have studied three moisture protective coatings: Eudragit L30D-55, Opaddry AMB and Sepifilm®. The study showed that Sepifilm® coating has the fastest water absorbance and the most hygroscopicity while Eudragit has the least hygroscopicity. This study shows that hygroscopic coating on a hygroscope core is more efficient in reduction of water intake by the core and hydrolysis of active ingredients (15).

Conclusion

Moisture-resistant polymeric coating is the usual method to protect drugs against deterioration by moisture. While almost all of the moisture protective coatings are hydrophobic and insoluble in water, they can cause reduction in drug release rate from dosage form, therefore poor bioavailability. Combination of hydrophilic polymers and hydrophobic components is an acceptable way to balance moisture protective properties and achieve fast release of drugs. The results of this study showed that presence of microcrystalline cellulose in HPMC free films as an insoluble component with high water absorbance could be effective on reducing moisture transmission through films by scavenging the moisture. Also using stearic acid as a hydrophobic plasticizer had a significant effect on lowering permeation of moisture through coatings and improved their mechanical properties. Film formulation containing 30% Avicel and 5% stearic acid could lead reduction in hydrolysis of aspirin in coated tablets which was almost similar to Sepifilm®

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