Study The Variables Affecting Formulation of Ethylcellulose-based Microsponges Loaded with Clobetasol [#]

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[#] 2nd Scientific Conference for Postgraduate Students Researches.
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Abstract

Microsponge (Msg) is a unique three-dimensional microstructure particle with micro and nano-meters-wide cavities, which can encapsulate both hydrophilic and lipophilic drugs providing increased efficacy and safety. Clobetasol propionate (CP) is a super potent corticosteroid widely used to treat various skin disorders such as atopic dermatitis and psoriasis. However, its utility for topical application is hampered due to its common side effects, such as skin atrophy, steroidal acne, hypopigmentation, and allergic contact dermatitis. The aim of the current study is to prepare and optimize clobetasol-loaded microsponges. The emulsion solvent diffusion method is used for the preparation of ethylcellulose (EC)-based microsponges. The impact of various formulation variables on microsponge's properties includes; drug: polymer ratio, polyvinyl alcohol (PVA) quantities, the volume of external aqueous phase, and stirring rates investigated. The microsponges were characterized in terms of particle size, product yield, CP entrapment %, and *in-vitro* drug release behavior. The results reported that increasing EC concentration led to a significant increase in particle size, with a decrease in product yield and drug entrapment %. Increasing stirring speed led to significant decrease in product yield; entrapment efficiency and particle size. While increasing PVA concentration or external volume caused a non-significant decrease in product yield and entrapment % but they showed a significant increase in particle size, respectively. The microscopic observation revealed uniform, highly porous particles. Finally, it was concluded that the ability to use ethylcellulose as a Msg polymer matrix for loading CP which will be formulated as topical hydrogel in a future research.

Key words: Clobetasol propionate, Ethylcellulose, microsponges, in vitro release

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دراسة المتغيرات التي تؤثر على صياغة الإسفنجات الدقيقة القائمة على الإيثيل السليلوز المحملة بالكلوبيتاسول

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الخلاصة

الاسفنجيات المايكرويه هي عبارة عن جسيمات مجهرية ثلاثية الأبعاد فريدة من نوعها مع تجاويف وفتحات متناهية الصغر بعرض النانو و المايكرومتر ، والتي يمكن أن تغلف كل من الأدوية المحبة للماء والأدوية المحبة للدهون مما يوفر مزيدًا من الفعالية والأمان. ان عقار كلوبتاسول بروبيونيت هو من الستيرويدات القوية التي تستخدم لعلاج اضطرابات الجلد المختلفة مثل التهاب الجلد التأتبي والصدفية. ومع ذلك ، فان هناك إعاقة لفائدته بعد وضعه على الجلد بسبب آثاره الجانبية الشائعة ، مثل ضمور الجلد وحب الشباب الستيرويدي ونقص التصبغ والتهاب الجلد التماسي التحسسي. لذلك فان الهدف من الدراسة الحالية هو إعداد وتحسين الاسفنجات المايكرويه المحملة بالكلوبيتاسول . استخدمت طريقة نشر المذيب المستحلب لتحضير الإسفنجات الدقيقة القائمة على إيثيل سيليلوز، وشملت الدراسه تقييم تأثير متغيرات الصياغة المختلفة على خصائص الاسفنجيات المايكرويه كنسبه العقارعلى نسبه البولمر, وتركيزكحول البولي فنيل ، وسرعة التحريك ، وحجم الطور المائي الخارجي. تم تمييز الاسفنجات المايكروية من حيث حجم الجسيمات ، والحصيلة الانتاجية ، ونسبة الدواء المحمل ، وتحرر الدواء في المختبر. بينت النتائج أن زيادة تركيز ايثيل سيليلوز أدى إلى زيادة معنوية في حجم الجسيمات ، مع انخفاض في الحصيلة الإنتاجية ونسبة تحميل الدواء. بينما ادت زيادة سرعة التحريك إلى انخفاض كبير في الإنتاجية ؛ كفاءة التحميل وحجم الجسيمات: في حين أن زيادة تركيز كحول البولي فنيل أو حجم الطور المائي الخارجي تسبب في انخفاض غير معنوي في الإنتاجية ونسبة تحميل العقار ولكنهم أظهروا زيادة معنويَّة في حجم الجسيمات، على التوالي. اظهر الفحص المجهري ان الجسيمات الاسفنجية المتكونة كانت متجانسة وعالية المسامية. مما تقدم نستنتج بانه من الممكن استخدام إيثيل السليلوز كبوليمر لتحضير الاسفنجات المايكروية المحملة بعقار كلوبتاسول والتي سيتم صياغتها بشكل هيدروجيل موضعي في بحث مستقبلي.

الكلمات المفتاحية : كلوبتاسول بروبيونيت, ايثيل السليلوز, الاسفنجات المايكروية, تحرر الدواء في المختبر.

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Introduction

Microsponges (Msg) are sponge-like particles spherical in shape along with plenty of interconnecting voids in a n on-collapsible matrix [1, 2]. Each Msg particle has ranged from 5-300 microns in size. The interior pore structure of 25μm, particle has approximately 2,50,000 pores with an internal pore structure equal to a length of about 10ft which allows 1ml/g pore volume for massive drug retention [3].

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Msg particles can be loaded quickly by diffusion, and the entrapped drug is released when came in contact with the skin [4]. Msg provides many benefits over other delivery systems, such as control drug release and improvement of physicochemical and thermal drug stability [5,6]. The Msg delivery system can significantly reduce drug irritation without reducing its efficacy, as seen when lornoxicam prepared as Msg, it succeeded in arthritic pain management through sustaining lornoxicam anti-inflammatory effects after loading it in cellulosic microsponge gel [7].Topical Msg prevents drug penetration into the subcutaneous layer, thus preventing its irritation effect [8].

Clobetasol propionate (CP) is super potent corticosteroid [9]. It is widely used to treat various skin disorders, including vitiligo, atopic dermatitis, pruritic eczema, and psoriasis. However, it has many side effects when applied to the skin, like skin atrophy, hypopigmentation, steroidal acne, and allergic contact dermatitis [10]. CP belongs to class 2 in BCS, means it has low solubility and high permeability. CP is white to creamy-white crystalline powder. Its melting point is 195.5_197 °C; practically insoluble in water; soluble 1 in 100 of ethanol and 1 in 1000 of ether. Log P (octanol/water) is 3.5 [11].

The aim of this study is to incorporate CP in ethylcellulose microsponges; different formulation variables include (drug/polymer) ratio; emulsifying agent ratio; stirring speed and volume of aqueous (external) phase were studied to maximize product yield; release profile and minimize particle size. Ethylcellouse is used as a polymer because of its stability, flexibility, and low cost.

Materials and Method
Materials
Clobetasol-17 propionate (CP) and ethylcellouse (EC) were kindly gifted by Samara Drug Industry; Samara; Iraq. Polyvinyl alcohol (PVA) was purchased from Indian fine chemical, India. Dichloromethane and methanol were purchased from loba chem, India, both of which are HPLC grade; no further purification was done. Dialysis bag MWco 8000-14000 D was purchased from Special product laboratory, USA. Potassium dihydrogen phosphate, Disodium hydrogen phosphate, and Micro porous membrane 0.22mcm were also used.

Method
Preparation of clobetasol microsponges
Eleven CP microsponge formulas were prepared to study the effect of different formulation variables on Msg properties, as summarized and shown in Table 1. Quasi-emulsion solvent diffusion method is used to prepare all CP microsponge [12]. Internal phase was prepared by dissolving CP and ethylcellulose in 5 ml dichloromethane by sonication using an ultrasonic shaker (Copley Scientific, UK); the external phase consists of PVA(polyvinyl alcohol) dissolved in 50 ml distilled water; the internal phase is added dropwise to the external phase with stirring for 2 hours using hot plate magnetic stirrer (Joan lab; China) at different stirring rate (500;1000;1500 rpm) at which the organic solvent could evaporate, and solid microsponge will precipitate; the resulted MS will be collected using Buchner funnel device with a vacuum pump (Kennedy manufacturing; USA) and was washed three times with distilled water then left to dry at 40°C in the oven (Memmert; Germany) for 12 hours. Figure 1 shows the steps used to prepare CP microsponge.

Figure 1.Quasi-emulsion solvent diffusion method for CP microsponges preparation "Created with BioRender.com" (Source: personal collection)

Table 1.Composition of Different CP-loaded Ethylcellulose Microsponges

Formula code.	Drug: polymer ratio	Aqueous(external) phase volume (ml)	Stirring rate (rpm)	PVA concentration (w/v %)
F1	2:1	50	500	0.25
F2	1:1	50	500	0.25
F3	1:2	50	500	0.25
F4	1:4	50	500	0.25
F5	1:1	50	1000	0.25
F6	1:1	50	1500	0.25
F7	1:1	100	500	0.25
F8	1:1	150	500	0.25
F9	1:1	50	500	0.15
F10	1:1	50	500	0.35
F11	1:1	50	500	0.45

*all formulations prepared with the amount of drug 300 mg except F1 add 600 mg, and the organic phase kept constant at 5ml dichloromethane and stirring time at 2h.

Characterization of CP microsponge-prepared formulations

Determination production yield

Production yield (PY%) was obtained by weighting the dry formula and dividing the final weight of the formula by the total weight of the drug and polymer as given by the following equation [13]:

$$PY\% = \frac{practical\ weight\ of\ microsponge}{theoratical\ weight\ (polymer+drug)} \times 100\%$$

Determination of particle diameter

The particle diameter of CP microsponge particles was determined using an optical microscope equipped with a graduated eyepiece used with a stage micrometer under polarized light [11]; the instrument was calibrated and found that one eyepiece is equal to 15 micrometers under 10X magnification then after calibration, the stage micrometer was replaced with a clean glass slide on which a little amount of CP Msg was uniformly dispersed as a thin layer; the average particle size was calculated by measuring 100 particles with the aid of ImageJ program for image analysis.

The average particle diameter was determined using the following equation: $D_{av} = \frac{\sum nd}{\sum n}$

Where: D_{av} is the particle's average diameter of (µm), n is the number of particles per group, and d is the middle value (µm).

Solid-state characterization of CP microsponge

Both differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR) analysis was used to evaluate the physical characters of CP-Msg in order to ensure purity and the absence of drug-excipient interaction; it was performed for the drug alone; selected polymer, physical mixture of both drug and a selected polymer, and the optimized Msg formula.

Thermal analysis was done using DSC (DSC-600, Shimadzu, Japan) by load 5 mg of the powder into an aluminum pan, then the pan is sealed, which was compared with a sealed blank aluminum crucible as reference. The temperature was elevated from 25°C to 300°C in a nitrogen atmosphere at the rate of 10°C per minute. The flow rate of nitrogen was 50 ml per minute. DSC indicates thermal compatibility between drug and polymer during the formulation of Msg and is also used to assess the crystalline state of the drug [14].

The IR spectrum was recorded using FTIR (FTIR600; Shimadzu, Japan). The sample was directly placed onto a modified crystal on FTIR instrument without any previous sample preparation, and the FTIR spectra were collected in the range of 4000–400 cm^{-1} [14,15].

Scanning electron microscope (SEM) study

Particle morphology and surface topography estimation was done using SEM (Thermo Fisher; Axia ChemiSEM). The samples were first sprinkled on double side carbon tape and then tight all stubs on the specimen's holder with simple blowing to remove particles that did not adhere. The prepared samples were loaded on SEM via an air-lock door which depends on low voltage to avoid charging [16].

Accelerated In-vitro release study

The dialysis bag technique was used to study the drug release rate from CP-Msg. The dissolution media consisted of 250 ml phosphate buffer(having a pH of 5.5. and 20% methanol) to maintain sink condition, 5 mg samples of CP microsponge were suspended in 2 ml phosphate buffer (pH 5.5 used to mimic the pH of the skin) in a dialysis bag, and the rotation speed was adjusted at 50 rpm and the temperature was 37°C. At prescheduled time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12h). Five milliliters of the media were withdrawn and replaced by an equal volume of dissolution medium to maintain a constant volume. The samples were analyzed at 242 nm using a double-beam spectrophotometer (Carry100 UV, Varian, Australia) [17].

Statistical analysis

Statistical analysis was done using one way ANOVA test add-in Microsoft Excel 2010; the difference was considered significant if P<0.05. Also, the standard deviation was calculated for each result [18].

Result and Discussion

Preparation of clobetasol microsponges

In this study, Ethylcellouse (EC) polymer was chosen to be the matrix-forming agent in formulations. The reason behind this selection is the availability and low cost of EC compared to others; good compatibility between EC with CP. The EC has attracted interest in controlled drug delivery systems due to its low solubility in water and biological matrix. Furthermore, because of the lower water uptake of EC, the release rate of the drug in formulations was decreased [19].

Dichloromethane was used as an internal phase organic solvent because it is a good solvent for both the drug and the polymer, in addition to its easy evaporation after diffusion, leaving a solid CP microsponge. Quasi-emulsion solvent diffusion method was used since it is easy to perform [20].

Characterization of CP microsponge-prepared formulations

The effect of several formulation variables on Msg properties, including production yield, % drug entrapment, and particle diameter, were displayed in Table 2 and discussed as the following:

Table 2. Characterization of Microsponges formulas

Formula code	Product yield %	Drug Entrapment %	Particle diameter
F1	77.77±0.6	77.41 ±2.04	55.97± 0.9
F2	69.00±0.8	64.7±1.56	62.51±1.5
F3	68.27±0.6	42.79 ±1.40	66.39±1.4
F4	67.9±1.5	23.93 ±0.52	83.21 ±1
F5	61.00±0.6	63.67±1.02	23.60 ±1
F6	59.42±1.5	56.08±0.60	22.47 ±1.9
F7	67.7±1	61.82 ±2.56	80.90 ±1.7
F8	64.3±0.7	61.52 ±0.78	109.22 ±1.3
F9	69.4±1.6	70.07 ±1.88	59.50 ±0.4
F10	62.83±1.5	62.96 ±1.90	75.18 ±0.5
F11	62.08±0.9	56.53 ±0.30	93.85 ±2.3

Effect of drug: polymer ratio

Figure 2 revealed evaluation data, as seen for formulas from F1 to F4; it was shown that when the polymer: drug ratio increases, the particle size will increase; this is because when increasing polymer: drug ratio, more amount of the polymer will be available to form CP-Msg which will increase the thickness of polymer will leading to the formation of large size Msg [21].

On the other hand, increasing polymer concentration leads to a significant decrease (P < 0.05) in drug entrapment % from (77.41 % ±2.04) to (23.93 % ±0.52) as the drug: polymer ratio increase from F1(1:0.5) to F4 (1:4) formulas. This result could be attributed to the increasing in viscosity due to increasing the polymer concentration which led to formation of more rigid polymer coat and difficulty of drug transfer with more viscous medium resulted in low drug entrapment % [22].

The production yield percent is highly correlated with the entrapment efficiency, as showed drug entrapment % had the same behavior as product yield; when increasing the polymer: drug ratio led to a significant decrease (p< 0.05) in production yield from 77.77% to 69.0% for formula F1 and F2, respectively. This may be explained by the fact that decreasing the amount of polymer concurrently increase drug amount used leading to decrease the viscosity of the medium, which allows easier diffusion of drug moiety and the formation of a more flexible polymer coat [23].
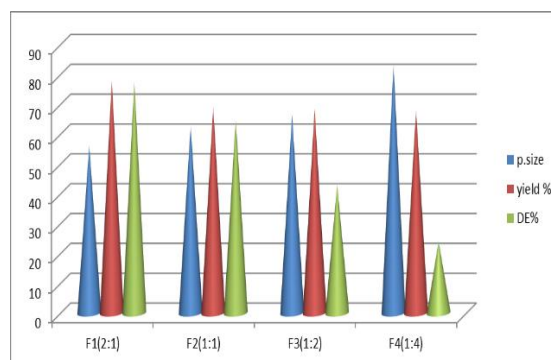

Figure 2.Effect of drug: polymer ratio on clobetasol microsponge properties

Effect of stirring rate

Comparing the characterization data as shown in Figure 3 of formulas F2; F5, and F6, which were prepared using the stirring rate at 500; 1000; 1500 rpm, respectively, showed that increasing stirring rate significantly reduced (p< 0.05) particle size. This may be due to the tendency of particles to aggregate at a low stirring rate, but when the stirring rate increase, the shear force will also increase, leading to the rapid dispersion of particles away from each other and less aggregation occur [24].

Product yield and drug entrapment % were decreased with increasing stirring rate. This can be related to the fact that increasing the stir rate lead to the loss of polymer particles by sticking to the wall of the beaker due to high shear force [25].The effect of stirring rate on product yield, drug loading, and particle size is significant (P< 0.05) as a result of the vigorous turbulence within external phase created at higher speed.
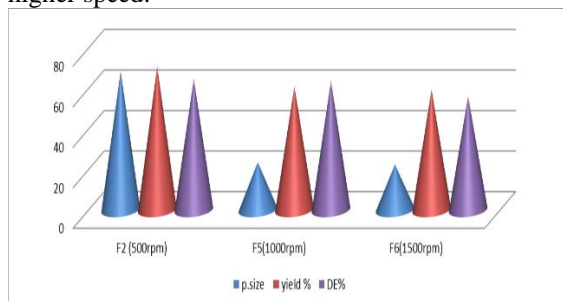

Figure 3. Effect of three different stirring rates on clobetasol microsponge properties

Effect of external phase volume

The external phase used is distilled water for easy Msg formation because clobetasol is practically insoluble in water. While increasing external volume from 50ml to 100ml, and 150ml for formulas F2; F7, and F8, respectively, and the concentration of PVA was kept constant. The results revealed, as shown in Figure 4, a significant (p< 0.05) increase in particle diameter. It was reported that microsponges particle size were directly proportional to the difference in apparent viscosity between the dispersed and continuous phase. when more viscous internal phase is poured into the continuous phase (external phase), the globules of the formed emulsion can hardly be divided into smaller particles and bigger droplets are found resulting in an increase in mean particle [26]. In addition to that, it was found that an increase in the external phase volume led to a non-significant (p>0.05) decrease in both product yield and drug entrapment% these results were in agreement with that found by Neamah and Maraie [27].
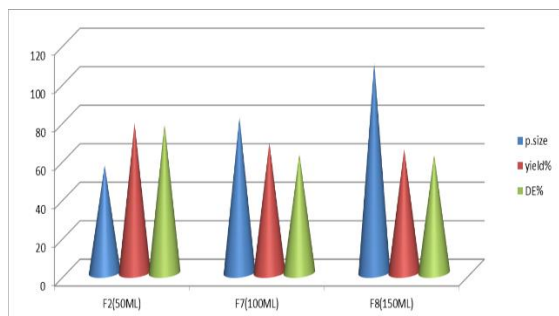

Figure 4.Effect of external aqueous phase volume on clobetasol microsponge properties

Effect of emulsifier concentration percent

PVA is used as an emulsifying agent to reduce surface interfacial tension. Increasing PVA

concentration in formulas F2; F9; F10; F11 while keeping polymer concentration constant leads to a decrease in drug entrapment % that is because the high concentration of PVA leads to increase Msg pore, which leads to more drug leaching [28]. It is also caused decreasing in product yield, as noticed in Figure 5, which may be due to PVA being non-ionic and clobetasol being hydrophobic; a higher amount of PVA hydrophobic region will form, which causes some amount of the drug to dissolve, leading to reduce product yield [29]. The effect on product yield and drug entrapment was found to be non-significant with (p >0.05). Additionally, increasing the PVA amount causes an increased viscosity of the emulsion that results in higher droplet size [30].

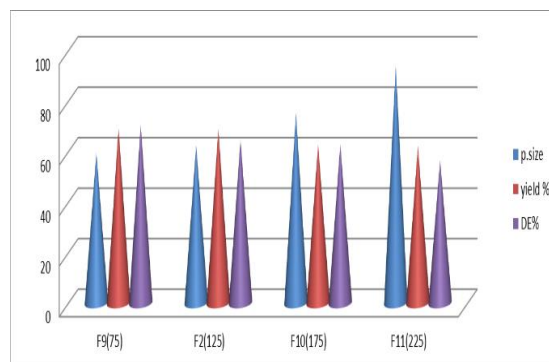
Figure 5. Effect of PVA on clobetasol microsponge properties

Selection of optimized formulation

Microsponge formulation with the highest product yield and drug entrapment; with small particle size and uniform particles morphology under optical microscopic examination was chosen for further evaluation. F1 was chosen as the optimized formula.

Solid-state characterization of CP microsponges

DSC thermogram of pure CP showed that CP having a sharp endothermic peak at 198℃ corresponds to the melting point of CP in crystal form [11]. EC polymer has a two-glass transition temperature (T_g at 128.7℃ and 223.3℃) in amorphous form. The presence of CP peak in the physical mixture was excluded from any interaction. For the selected formula (F1), the DSC thermo gram revealed the disappearance of the CP peak, while EC peaks are present, indicates the uniform dispersion of CP in the formula matrix, as shown in Figure 6.
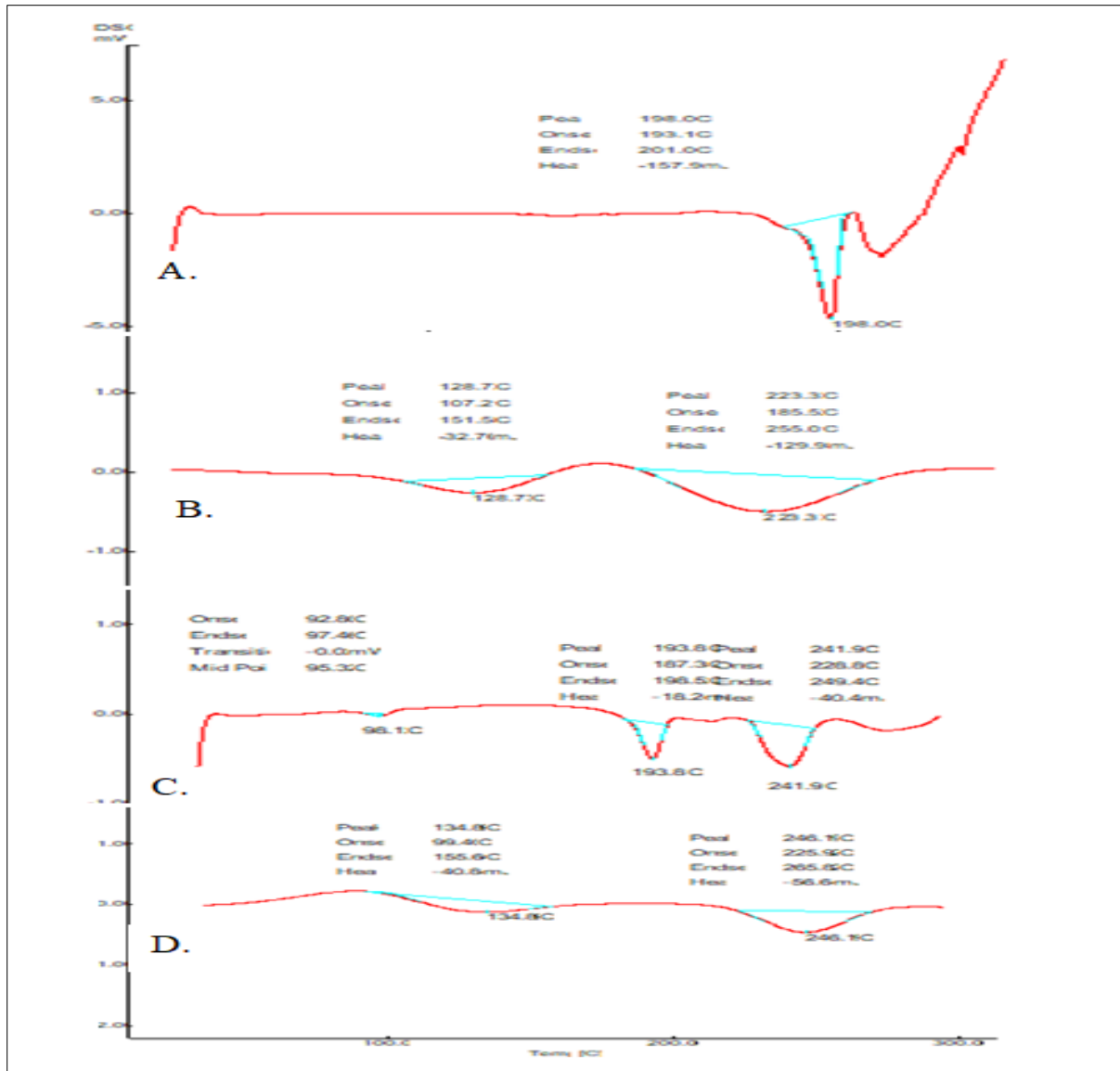
Figure 6. Thermogram obtained by DSC for A) pure CP, B) Ethylcelloluse, C) physical mixture D) formula (F1) microsponges

On the other hand, the peaks obtained from FTIR analysis for pure CP were recorded and shown in Table 3.

Table 3. The Characteristics FTIR Peaks and Their Interpretation of Pure Clobetasol .

FTIR peaks (cm^{-1})	interpretation
1662.64	C-F stretching of the ester
1604.77	C=C stretching of ketone
1732.08	C=O stretching vibration of ester
1458.18	C=C stretch
2943.37	C-H stretch of alkane

EC has a strong peak at 1056; This is for C-O stretching of ether; also peak at 2974 indicates sp^3 C-H stretching;   2873 represents symmetric C-H stretching. The characteristic absorption bands of the drug were observed in the physical mixture, and the optimum formula (F1) indicates compatibility and no interaction present [31], as shown in Figure 7.
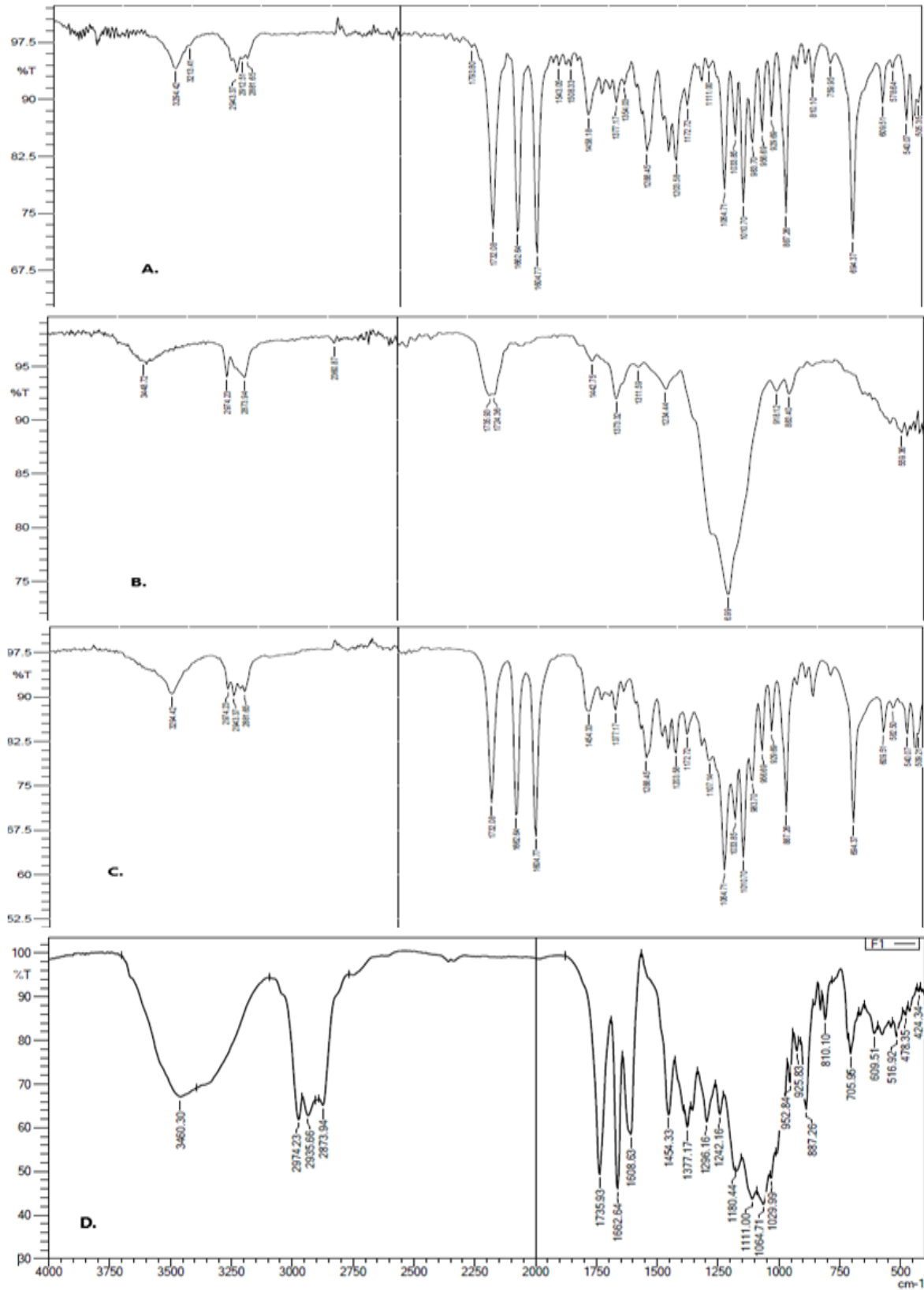
Figure 7. FTIR spectra of A) pure drug, B) EC, C)physical mixture of drug+EC and D) formula F1

Scanning electronic microscope (SEM)

SEM analysis of pure drug illustrated the crystal structure of CP, which was confirmed by DSC thermogram. The SEM analysis of formula F1 showed spherical porous particles with uniform size and shape; the surface has many pores, as this is the effect of solvent diffusion (Figure 8).
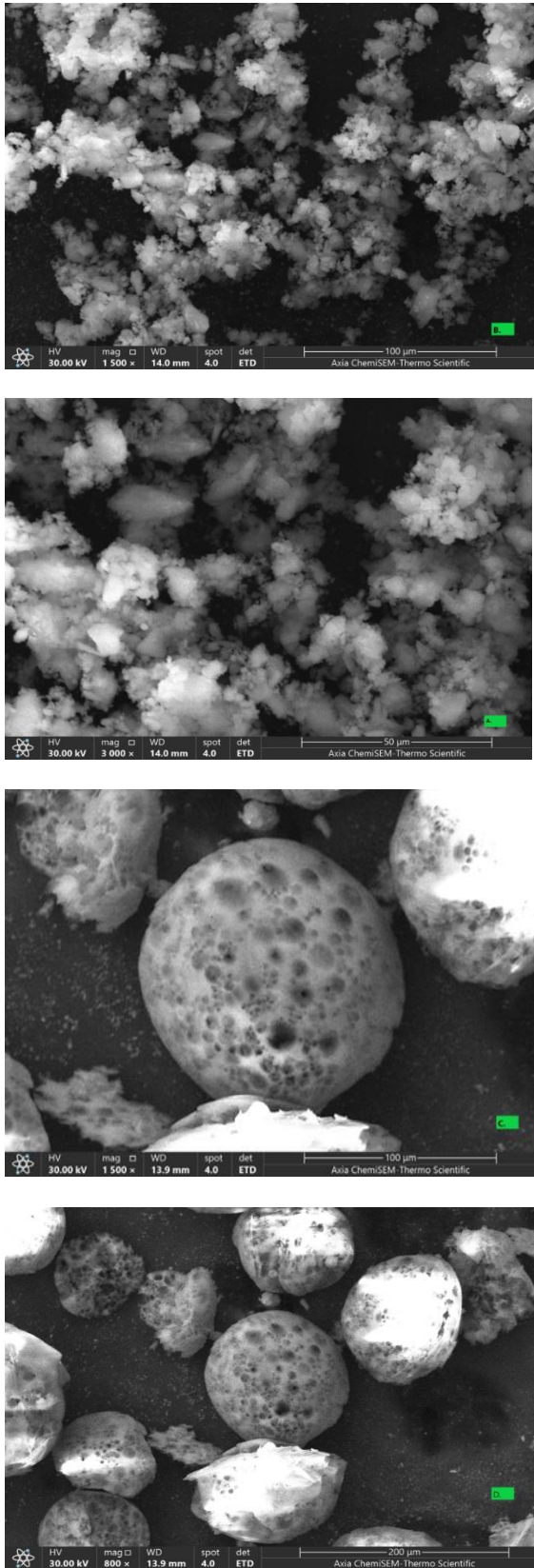
Figure 8. SEM pictures of A) CP at 3000 magnification (mag). B) CP at 1500 mag. C) F1 at 1500 mag. D) F1 at 800 mag.

In-vitro drug release study

Figure 9 showed CP % released at two polymer ratios (formulas F1(2:1) and F2 (1:1)) in comparison with the release of pure drug suspension. The result showed that F2 has sustained release compared to F1 this because an increased polymer ratio leads to an increase in particle size; large particles mean less effective surface area leading to a long traveling path for the drug to be released [31]. For both formula had better release than a pure drug; this can due to increasing drug dissolution when incorporated in Mgs which may be attributed to the fact that the reduction of drug particle size caused an increase in the surface area and consequently enhances the contact between particles and dissolution medium. The obtained results are in good accordance with Noyes–Whitney equation which states that the decrease in particle size lead to an increased dissolution rate [32].
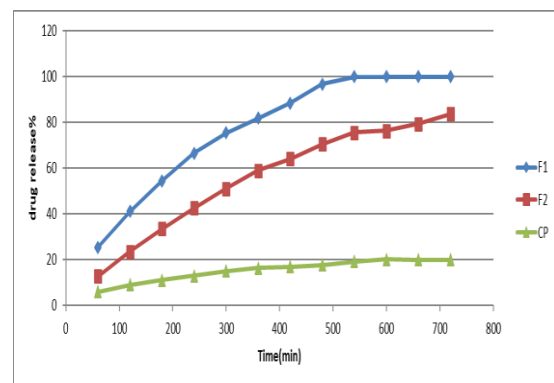

Figure 9.The % drug released from formulas F1 and F2 compared to a pure drug suspension

Conclusion

From this study, it can be concluded that the ability to use ethylcellous as a Msg polymer matrix to prepare uniform, highly porous particles and compatibility with CP. The study formulation variable including drug: polymer ratio and stirring rate have a significant impact on microsponges particle size, product yield and % drug entrapment efficiency.

Funding

No funding support

Ethics Statements

The research did not include any study on animal or human

Conflict of interest

We declare that there are no conflicts of interest.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: Lubna A .Sabri (L.A.S.); data collection: Ahmed Saad (A.S); analysis and interpretation of results: L.A.S, A.S; draft manuscript preparation: L.A.S,

A.S. All authors reviewed the results and approved the final version of the manuscript.

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