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Preparation of Superporous Hydrogel Composites Drug Delivery System Using Metronidazole as a Model Drug

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ABSTRACT

The aim of this study is to prepare gastroretentive dosage form based on the super porous hydrogel (SPH) composites using metronidazole as a model drug for eradication of *H pylori*.Blowing technique was used to prepare SPH composites. The latter was used as a body for the drug delivery system. The core was made from matrix granules. Four types of retardants (Beeswax, carnauba wax, ethylcellulose, and Eudragit®RS) were used to prepare the granules by fusion for waxes and wet granulation methods for other polymers. For each retardants, two ratios (1:1 and 1:0.5 of drug: retardant) were used. Simple new method for insertion of core inside the SPH composite by using syringe with wide end opening without use of glue to close the insertion site was applied. The system was characterized by scanning electron microscopy, FT-IR. Also swelling, mechanical, and dissolution properties were studied. Scanning electron microscopic images clearly show highly porous structure and interconnected channels. FT-IR study confirmed the formation of crosslinking poly (acrylamide- sulfopropyl acrylate) SPH composites. The delivery system achieved the equilibrium swelling in about 3 minutes with swelling ratio of 10.45 ± 0.9 and penetration pressure of 483.34 ± 48.0 cm H_2O. The results showed non-significant ($p > 0.05$) difference between loaded and unloaded SPH composites regarding mechanical and swelling properties. A significant difference ($P < 0.05$) was found among the cumulative amount of metronidazole released with time depending on the nature and ratio of each retardant. It can be concluded that the proposed drug delivery system based on superporous hydrogel composite is promising for gastroretentive stomach specific delivery of metronidazole.

Key words: Superporous hydrogel composites, Gastroretentive dosage form, metronidazole

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INTRODUCTION

Oral administration of controlled release systems represents a very attractive approach for drug delivery which is preferred to the other routes. It is still a big challenge to formulation scientists due to the difficulties associated with restriction and localization of the system to targeted area of the gastrointestinal tract[1,2]. Gastroretentive dosage form regards a promising dosage that is taking more and more attention for its advantage in permitting control over the time and site of drug release[3]. Over the last years, to prolong the gastric residence time, many gastroretentive dosage forms have been designed[4].They may be broadly classified into high density systems, floating systems, expandable systems, superporous hydrogels (SPHs), mucoadhesive or bioadhesive systems, magnetic systems, and dual working systems[5].

SPHs are porous structures usually prepared from hydrophilic crosslinked polymers, characterized by their ability to absorb aqueous fluids up to a few hundred times their own weight[6]. The pore in the SPHs is larger than 100µm, usually in the range of several hundred micrometers and can be up to the millimeter range. The interconnection of pores inside of the SPH to form an open channel system allows the dried SPH to absorb water by capillary wetting rather than by diffusion which ensures fast swelling of SPH[7].

In order to improve the mechanical properties of SPH, the second (SPH composites) and third (SPH hybrid) generation of SPHs were developed[8]. SPH composites possess important properties to be used as an effective gastric retention device which include [6]:

- Short swelling time (i.e. swelling to equilibrium size in 20 min or less).
- Large Swelling ratio (swell to a several times of its dry size).
- Good mechanical strength (enough to overcome pressures by gastric contractions.

The maximum gastric pressure in the fasted and fed states is known to range from 100 to 130 cm H_2O in humans[9]).

Although it is not quite clear whether antimicrobial drugs act locally in the stomach or after systemic absorption, complete eradication of *H. pylori* is currently considered to be difficult due to the short residence time of the available oral drugs in the stomach. But it is thought that continuous local delivery to the stomach could be useful for *H. pylori* eradication[10,11].

It was therefore tried to improve local delivery to the stomach using several gastroretentive dosage forms and variable degrees of success were obtained[12].

These dosage forms prolong the gastric residence time, decrease the diffusional distance, and allow more of the antibiotic to penetrate through the gastric mucus layer and act locally at the

infectious site. Increasing local concentration and contact time also can contribute to minimizing antibiotic resistance associated with systemic administration[13].

The aim of this investigation is to prepare a gastroretentive dosage form based on the SPH composites using metronidazole as model drug for eradication of *H. pylori*. The study includes the preparation of SPH composites, characterization of prepared SPH composites, in addition to study of loading and release of metronidazole.

MATERIALS AND METHODS

Materials

Acrylamide (AM), acrylic acid (AA), potassium salt of 3-sulfopropyl acrylate (SPAK), *N*,*N*′-methylenebisacrylamide (Bis), ammonium persulfate (APS), and *N*,*N*,*N*′,*N*′-tetramethyl-ethylenediamine (TEMED) were purchased from Himedia limited, India. Metronidazole, croscarmellose sodium, bees wax, carnauba wax, and ethylcellulose were gifted from Nineveh drug industry, Iraq. Eudragit RS and Pluronic F-127 were purchased from Sigma chemical co. (Aldrich). $NaHCO_3$, hydrochloric acid, potassium dihydrogen phosphate, methanol, and ethanol (99.8% absolute) were obtained from BDH Chemicals Ltd Poole, England.

Preparation of Superporous Hydrogel Composite

The synthesis of SPH composite was carried out by solution polymerization of the monomers using gas-blowing technique as described by chen *et al*.[14] with some modification.

The following components were added sequentially to the test tube: 1200 µl of 50% AM; 900µl of 50% SPAK; 450 µl of 2.5% Bis; 90 µl of 10% Pluronic F127 (a foam stabilizer); 30 µl of 50% AA; and 45 µl 20% APS. The solvent used was deionized water. The test tube was shaken to mix the solution after each ingredient was added. Then 270 mg of croscarmellose powder was added to the mixture, which was stirred using a glass rod.

Then, 45 µl of 20% TEMED was added to the mixture and the test tube was shaken again. Finally, 100 mg of $NaHCO_3$ powder was added and the mixture was immediately stirred vigorously using a glass rod for 10 seconds.

Polymerization was accelerated after addition of $NaHCO_3$ and completed in a few minutes. The SPH was cured at room temperature for 10 minutes. The SPH was retrieved from the test tube, and washed in a beaker containing mixture of ethanol and water in a ratio of 3:1. The SPH was then dried at room temperature for 2-3 days.

Preparation of Superporous Hydrogel Composites based Drug Delivery System

The SPH composites based drug delivery system was prepared as a core inside the body of the

system as reported by Dorkoosh *et al*. with modifications[15], it is consisted of two components; the body of the system made of SPH composites and the core which contain metronidazole matrix granules.

In order to prepare the body of the system, firstly SPH composites were synthesized as described above, after washing and before the SPH composites was completely dried (to provide certain degree of elasticity) a special syringe with a wide end orifice was inserted to certain depth in prepared SPH composites, which allow to inject metronidazole matrix granules (equivalent to 200 mg metronidazole), then a piece of SPH composites was inserted tightly to act as a cap.

The drug matrix granules in the core (metronidazole) prepared with different retarding agents and different ratios as shown in table 1.

Table 1: Composition of different formulas of superporous hydrogel composites based drug delivery system

Formula NO.	Metronidazole	Metronidazole : Bees wax ratio	Metronidazole : Carnauba wax ratio	Metronidazole : Ethylcelullose ratio	Metronidazole : Eudrageit RS ratio
F1	200mg				
F2		1:1			
F3		1:0.5			
F4			1:1		
F5			1:0.5		
F6				1:1	
F7				1:0.5	
F8					1:1
F9					1:0.5

Preparation of waxy matrix granules

The matrices were prepared by hot fusion method where the waxes were melted with continuous stirring in a porcelain dish placed on a water bath maintained at approximately 65 and 85 $^{\circ}$C for bees and carnauba wax respectively. Metronidazole was added to the fused waxes with continuous stirring. The molten mass of each formulation was allowed to cool down and screened through a 0.8 mm sieve, when the temperature was at around the congealing point[16].

Preparation of polymeric matrix granules

Drug and polymer were mixed in the desired mass ratio manually for 10 minutes. Ethanol was used as the granulating liquid to form the wetted mass. The wetted mass was thoroughly blended until an adequate consistency for granulation was achieved and was then strained through a sieve with a nominal aperture of 0.8 mm. The prepared granules were dried at ambient temperature for 2 hours[17,18].

CHARACTERIZATION OF SPH COMPOSITES

Scanning electron microscope (SEM)

SPH composites were cut to expose their inner structure before analysis using Phenom™, Netherlands SEM

Fourier transform infrared spectroscopy (FT-IR)

The chemical structures of the synthesized SPH were investigated by using FT-IR spectroscopy (Shimadzu FTIR 8000, Japan). Disk samples were prepared for AM, SPAK, and dried prepared SPH with KBr. The spectra were scanned over a frequency range of 4,000–500 cm^{-1}.

Swelling studies

The dry SPH were allowed to swell in 0.1N HCl at 37 °C. The weight of the hydrating samples was measured at one minute interval, after excess water was removed by gentle blotting. The swelling ratio (Q) is defined as:

$$Q = (W_s - W_d) / W_d$$

Where

W_s is the weight of the swollen SPH

W_d is the weight of the dry SPH[15].

Mechanical strength study

The penetration pressure of the SPH composite was measured using a bench comparator as described by Chen *et al*. with modifications[15]. The fully swollen hydrogel was put longitudinally under the lower touch and weights were successively applied to the upper touch until the polymer completely fractured. The penetration pressure could be calculated from the following equation[19]

$$PP = W/S$$

Where,

PP is the penetration pressure,

W is the weights at complete breakage of the polymer

S is the area of the lower touch.

Entrapment efficiency of metronidazole in matrix granules

HPLC was used to determine the drug content in prepared granules in order to calculate the entrapment efficiency (EE). Fifty milligrams of well-powdered granules was shaken for 1.5 h after addition of mobile phase up to 100 ml in ultrasonic. The metronidazole content was determined in the filtrate and the EE % was calculated according to the following equation [16]:

$$\% EE = \text{(Actual drug content/theoretical drug content)} \times 100$$

The HPLC method as described in BP includes using C18 column (250 x 4.6 mm, 5 µm). The mobile phase was prepared by mixing 30 volumes of methanol and 70 volumes of a 1.36 g/l solution of potassium dihydrogen phosphate at a flow rate of 1 ml/min and wave length of 315.

***In vitro* dissolution studies**

The release of metronidazole was determined in USP XXX dissolution apparatus II. The dissolution test was performed using 900 ml of 0.1 N HCl at 37 ± 0.5˚C and 100 rpm. Volumes of 5 ml were withdrawn hourly from the dissolution medium and replaced with fresh medium. The filtered samples were analyzed spectrophotometrically for metronidazole at 276 nm (Carry UV, Varian, Australia).

Mathematical modeling of drug release profile

The *in vitro* drug release data of all the batches were subjected to kinetic analysis by fitting to different models as shown in table 2[20,21].

Table 2: Mathematical models for analysis of drug release

Zero order kinetic	$Q_t = Q_o - K_o t$
First order kinetic	$Q_t = Q_o e^{-k1t}$
Higuchi model	$Q_t / Q_\infty = k_H t^{1/2}$
Korsmeyer-Peppas model	$Q_t / Q_\infty = k_{kp} t^n$

*Q*t: amount of drug released in time t; *Q*0: initial amount of drug in the dosage form; *Q*∞: total amount of drug dissolved when the dosage form is exhausted. K_0, *K*1, *K*H, *K*s, *K*kp,: release rate constants; *n*: release exponent (indicative of drug release mechanism)

RESULTS AND DISCUSSION

Preparation of superporous hydrogel composites based drug delivery system

The procedure to prepare delivery system described by Dorkoosh *et al.* includes formation of hole inside of the SPH composites by use of a borer when the SPH composite was at the swollen state. Thereafter, they were dried. Then the core was incorporated inside the body of the conveyor system and this system was capped by a piece of SPH using biodegradable glue [15].

In this study the procedure of Dorkoosh was modified. Where, the washing with diluted ethanol prevents the complete dehydration of SPH composite and provide some degree of elasticity allow injecting the core inside the body of the system instead of formation the hole also the tight insertion of small piece SPH composite as cap cancel the need to the biodegradable glue Figure1.These modifications made the incorporation of core easy and avoid the problems associated with rapid or unequal drying process (e.g. cracking).The core was made of granulated metronidazole with retarding agent. In this study four retardants were used separatly, two waxes (bees wax or carnauba wax) and two polymers (ethylcellulose or Eudragit RS).

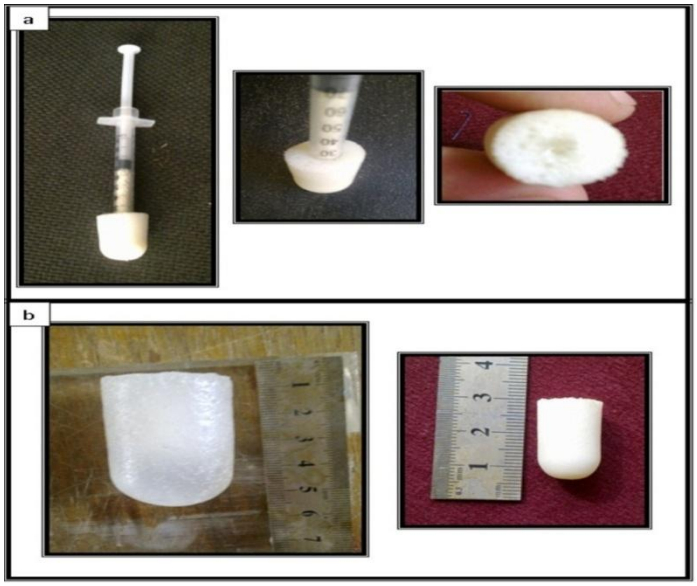

Figure 1. Photographs of the insertion process of core inside the SPH composite (a). SPH composite delivery system at swollen state (b).

Metronidazole waxy granules were prepared using fusion method because this method does not require solvent or water, since the molten wax acts like a binder.This method generally requires relatively high processing temperatures. The excipients and the active ingredients need to be stable under these conditions. Generally waxes are inert and have lower melting points than those of polymers [22]. On the other hands, wet granulation method was selected to prepare the polymeric granules. The entrapment efficiency of all batches of granules shows good results in the range of 92.9-102.2% table 3.

Table 3: %EE of different core granules

Formula no	%EE
F1	Pure drug
F2	94.8
F3	98.5
F4	92.9
F5	102.2
F6	99.1
F7	93.4
F8	101.6
F9	99.7

Characterization of SPH composites

Scanning electron microscope (SEM)

The scanning electron microscopic images of SPH composite Figure 2, shows clearly presence of large pores in the prepared SPH composite. The diameter of pores (about 225 µm) is in preferable pore size range according to Chen and Prak[7].

Also it can be noticed in the image that the pores are connected to each other to form extensive capillary channels, which help the dried gels swell to near equilibrium size in a matter of minutes[8].

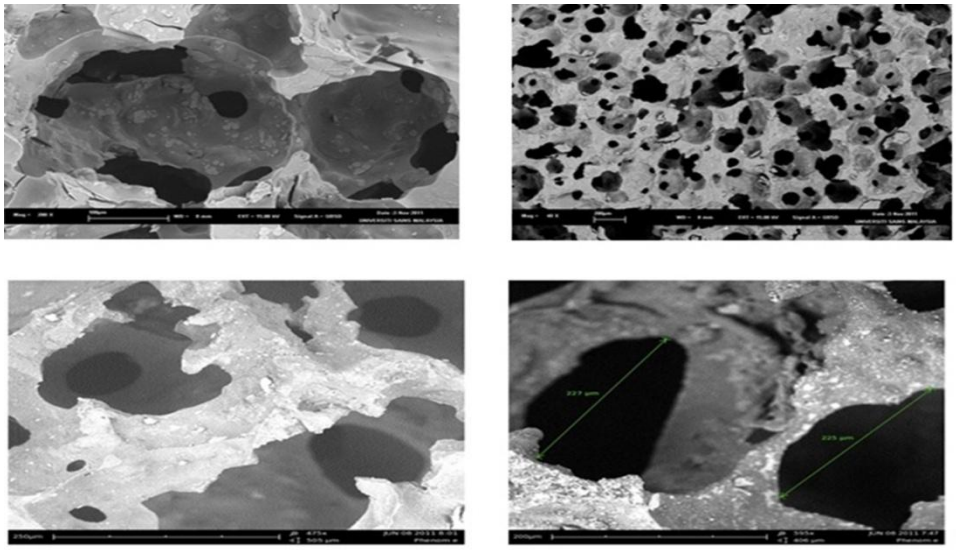

Figure 2. Scanning electron microscopic images of SPH composite

FT-IR study

The structural characterization of the SPH composites was performed by recording FT-IR spectra of the samples and compared with spectrum of pure monomers.

Figure 3 shows the spectra of AM, SPAK, and poly (AM-SPAK) SPH composite. Where, the major finding is the disappearance of the vibration band for C=C that appear initially at 1613cm^{-1} and 1636 cm^{-1} on AM and SPAK spectra respectively which confirms opening the double bond of vinyl monomers which then was bind to each other covalently. Also, the disappearance of =C-H stretching band at 3107 cm^{-1} confirms the opening of the double bond.

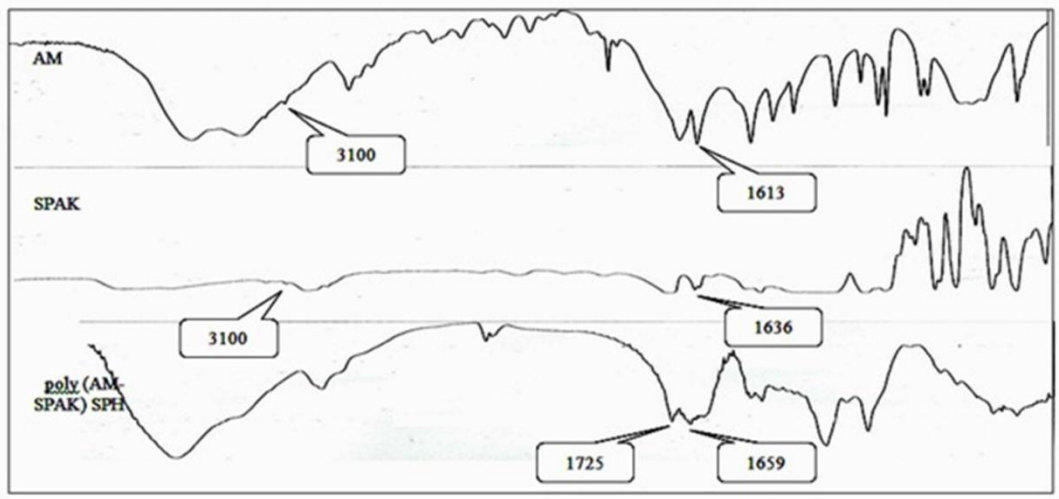

Figure 3. FT-IR spectra of SPH composite

The broad overlapped band at 1725 cm^{-1} and 1659 cm^{-1} for C=O stretching of ester (SPAK) and amide (AM) respectively was noticed on the spectra which indicates the occlusion of two monomers in the preparation of SPH composite.

Swelling and mechanical properties

The prepared SPH composite based delivery system was evaluated for swelling and mechanical properties. The results were compared with those obtained from blank SPH composite (befor insertion the core) as shown in table 4, no significant difference ($p > 0.05$) was reported between the properties of SPH composite based delivery system and blank one.To act as a gastric retention device, the SPH composite must be swell fast, less than 20 minute, to a large size enough to be retained in the stomach and overcome gastric emptying. The swelling time of prepared was much faster than that required for gastric retention with good swelling ratio. Since the pressure during the gastric contraction was reported to range from 50 -130 cm H_2O[9]. This value, however, reflects only the direct compression pressure but there is other forces, such as abrasion and shear forces, would increase the actual pressure on hydrogels. Thus, for a SPH to be maintained as an integral dosage form in the stomach, it must be able to withstand a pressure much higher than the 130 cm water pressure. The SPH composites drug delivery system shows good penetration pressure (483 cm H_2O) that ensures the ability to withstand gastric contraction pressure.

Table 4: Swelling and mechanical properties of SPH composites

	Swelling time to 90% (min)	Swelling ratio	Penetration pressure (cm H_2O)
Blank SPH	1	10.040 ± 1.6	548.446 ± 64.5
SPH composite DDS	3	10.459 ± 0.9	483.346 ± 48.0

***In vitro* dissolution studies**

The effect of SPH composite on the release profile of metronidazole from delivery system was investigated by using metronidazole powder alone as core in F1 figure 4. Generally, the drug release from SPH composite delivery system involve following steps: (i) wetting the SPH composite and water absorption through the interconnected channels with polymer swelling; (ii) drug dissolution; and (iii) drug diffusion out of the SPH composite. As discussed previously, step (i) was fast and its effect restricted to the first few minutes. So the extended release of F1 can explain by steps (ii) and (iii) mainly.

SPH composite act as a diffusional barrier against the dissolved drug (step iii) also SPH composite maintaining the drug particles aggregated and decrease the surface area for drug dissolution (step ii). Although the release time of metronidazole from SPH is extended, but still

not enough to provide sustained release action, thus additional retarding approach with matrix granules was used.

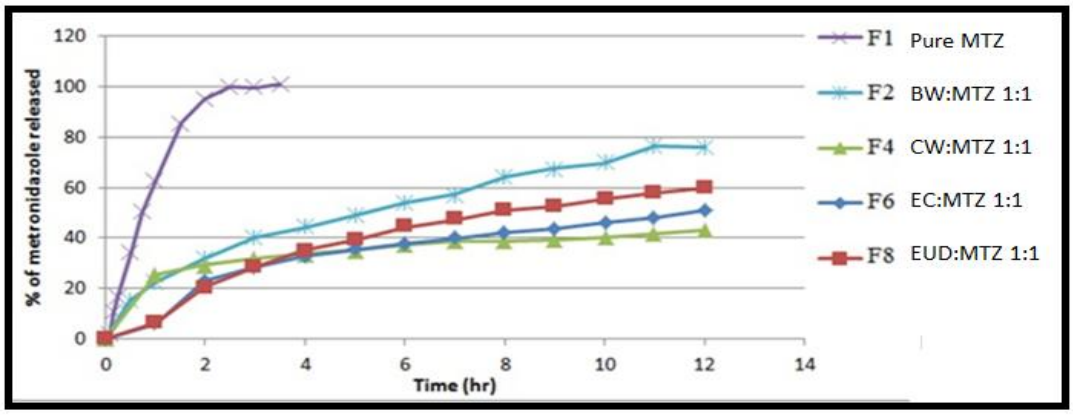

Figure 4.Effect of retarding agent (Bees wax, Carnauba wax, Ethylcellulose, Eudragit RS) on the release of metronidazole from different formulas in 0.1N HCl at 37 ºC

The release of metronidazole from formulas F2, F4, F6, and F8 which contain granules of (1:1) drug: retardant ratio for bees wax, carnauba wax, ethylcellulose, and Eudragit RS respectively is shown in figure 4. A significant difference ($P < 0.05$) was found among the cumulative amount of metronidazole released with time depending on the nature of each retardant and in comparison to F1.

Figure 5 shows the effect of retardant concentration on metronidazole release from the SPH composite delivery system. It was seen that there is a significant increase ($P< 0.05$) in the metronidazole release from SPH composite delivery system as a function of decreasing concentration of the retardants

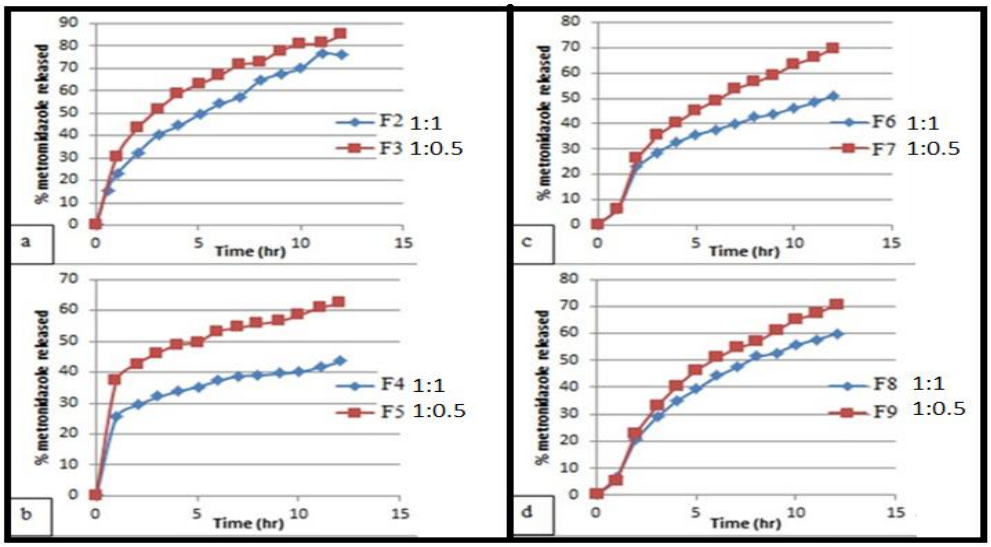

Figure 5. The release profile of metronidazole at different drug to retarding agent ratios (a) bees wax, (b) carnauba wax, (c) ethylcellulose, and (d) Eudragit RS in 0.1N HCl at 37 ºC

Although bees and carnauba wax had similar nature, they showed greatly different release rates. The release from carnauba wax core was very slow (43% after 12 h). It may be due to difference in chemical constituents, where carnauba wax is a more lipophilic matrix that hardly allows any water to penetrate into the pores of the matrix structure[23].

The release of metronidazole from carnuba wax core in SPH composite delivery system (F4 and F5) characterized by burst release through the first hour which may be due to the free drug remained outside granules[24].

In the case of polymeric retardants (F6 and F8 for ethylcellulose and Eudragit RS respectively), the release of metronidazole from ethylcellulose core was slower (51% after 12 h) than that form Eudragit RS core (59.7% after 12 h) as seen in figure 4.

This finding can be attributed to the water-repelling property of ethylcellulose (an inert hydrophobic polymer) which retarded drug release.

However Eudragit RS was hydrophilic polymer insoluble in aqueous media contain quaternary ammonium groups in their structure. These quaternary ammonium groups were solubilized in acidic pH leads to formation of pores in the matrix of polymer[25].

Among the four retarding agent Eudragit RS produces the best release profile in the initial and remaining time of 12 hrs.

Regarding the ratios of retarding agent, for a matrix system like granules that used in core of SPH composite delivery system, drug particles present in the surface of the matrix is initially released into the surrounding media generating many pores and cracks which facilitates further release of drug [26]. Therefore, a decrease in the retardants ratio results in faster drug release which may attributed to higher porosity and/or tortuosity.

Mathematical modeling of drug release profile

The release kinetics of metronidazole from the prepared SPH composite drug delivery was determined by finding the best fitting of the dissolution data to the mathematical models. In addition, analysis of the experimental data according to Korsmeyer-Peppas model with its interpretation of the corresponding release exponent values *n* leads to better understanding of the drug release mechanism.

Table 5 illustrates correlation of dissolution data to the different models of release kinetic, where a good fitting to the Higuchi model was observed for all formulas except for formulas F1, F7, andF9 which exhibited first order model. In addition, table 5 shows that ***n*** values of formulas F1and F9 are greater than 0.89 which indicate super case II transport, the ***n*** values of formulas F3 – F5 are less than 0.45, which means quasi Fickian diffusion mechanism. The other formulas

shown ***n*** values between 0.45 and 0.89, which mean anomalous (non-Fickian) diffusion mechanism.

Table 5: The kinetic analysis results of metronidazole release from different formulas SPH composite based drug delivery systems

Formula No.	Zero-order		First-order		Higuchi model		Korsmeyer - peppas model		
	K_0(mg hr^{-1})	R^2	K_1hr^{-1}	R^2	$K_Hhr^{-1/2}$	R^2	$K_{kp}(hr^{-n})$	n	R^2
F1	0.9386	0.8735	0.0130	**0.9767**	15.276	0.9600	0.6846	1.3132	0.9465
F2	11.281	0.9302	0.1133	0.9869	22.309	**0.9975**	0.2214	0.5036	0.9975
F3	11.299	0.8318	0.1403	0.9756	23.69	**0.9799**	0.3103	0.4424	0.9935
F4	5.5103	0.6283	0.0373	0.6986	11.244	**0.8665**	0.2541	0.2047	0.9947
F5	6.7610	0.6399	0.0576	0.7817	14.872	**0.8632**	0.3690	0.2008	0.9920
F6	7.4538	0.8614	0.0537	0.9230	15.231	**0.9638**	0.1010	0.7039	0.8492
F7	10.748	0.9063	0.0946	**0.9778**	21.514	0.9729	0.1051	0.8251	0.8693
F8	11.105	0.9131	0.0753	0.9692	19.041	**0.9762**	0.0961	0.8013	0.9186
F9	13.177	0.9163	0.0999	**0.9831**	22.396	0.9709	0.0878	0.9350	0.8842

CONCLUSION

The granulation of drug with retarding agent then insertion of granules (as a core) inside the SPH composite by our simple method produces successful gastroretentive drug delivery system based SPH composite with good does not affect the swelling, mechanical and dissolution profile.

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