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FUROSEMIDE LOADED SUPERPOROUS HYDROGEL COMPOSITE AS A CONTROLLED RELEASE DEVICE: DIFFERENT STRATEGIES FOR DRUG LOADING

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ABSTRACT

The aim of the present work was to develop controlled release, gastroretentive device using superporous hydrogel composite (SPHC). Furosemide was chosen as good candidate for such system due to its narrow absorption window, low bioavailability and short half-life. Plain hydrogel was evaluated with respect to swelling ratio, apparent density and floating time. Scanning electron micrographs of SPHC showed large interconnected pores and extensive capillary insertion. Prepared Microspheres were tested for drug content, and tablets evaluated with respect to quality control tests. All loaded formulae inside SPHC were tested for drug release profile. Microspheres, tablets and drug solutions were tested for loading inside SPHC. Kinetic treatment of release data revealed that soaked drug solution was unable to control drug release, where it gave a $t^{1/2}$(0.5hrs) very similar to that of the free drug (0.6hrs). Loaded microspheres showed only a slight retardation in release $t^{1/2}$ to 1.06 hrs along with a high percent of flush (~30mg %). However, loaded tablet demonstrated a promising sustained effect corresponding to a release $t^{1/2}$= 6hrs and a low percent of initial flush (~1.2mg %). Therefore, the applicability of SPHC as a controlled release device proved to be largely dependent on the type of dosage form included.

INTRODUCTION

Since drug delivery technology [1] is an equivalent component in drug development, a design of delivery systems that can target a candidate drug to its absorption site is a successful achievement [2-3].

Among the different systems and devices used to control the drug delivery to the GIT, gastroretentive dosage forms have attracted much attention of academic researchers [4]. Those systems are advantageous in case of drugs characterized by a narrow absorption window. They provide a prolonged intimate contact with the absorbing membrane; thereby, increasing efficacy [5].

For a successful development of a gastroretentive system, the selected dosage form must be able to reside for a time necessary to release the entire drug included before the normal physiology of the stomach can clear up the dosage form to the intestine [6].

Many attempts have been made to attain gastroretention through different systems including bioadhesion[7] or mucoadhesion to gastric mucosa [8-10], high density systems [11], floating systems[12-15], and expandable systems[16]. In our study, we focused specifically on superporous hydrogel systems, as the fast swelling[17] highly porous nature[18-20] of these devices made them excellent candidate materials for gastroretentive delivery of many drugs[5].

Owing to their unique properties, when applied as drug carriers, superporous hydrogels swell to a volume much larger than the opening of the pylorus[21]; thus, remaining in the stomach for the time necessary to release the loaded drug within their matrices before they begin to degrade [22].

The new technology found extensive pharmaceutical application. Dorkoosh etal succeeded to prepare superporous hydrogel polymers loaded with peptide drugs such as buserelin, octreotide and insulin, and proved that these devices were promising systems for peroral peptide drug delivery[23-24]. Later on, Yin etal were able to improve the intestinal absorption of insulin using superporous hydrogel containing interpenetrating polymer network (IPN) [25]. A more recent study achieved by Gümüşderelioğlu etal demonstrated the superiority of superporous polyacrylate/chitosan interpenetrating network hydrogels for protein delivery. Bovine serum albumin was taken as a model protein. Loading was performed by the soaking method before and after IPN formation[26].The method of soaking superporous hydrogels in drug solutions was also employed in loading rosiglitazone maleate on swelled polymeric matrix[27]. Mahmoud etal incorporated a self-nanoemulsifying drug delivery system into the SPHC matrix[28]. The incorporation of ranitidine hydrochloride and release retardant polymers in SPHC through a central hole was demonstrated by Chavda etal. A piece of SPHC was used to close the hole by the aid of biodegradable glue. The whole system was used to sustain the delivery of the drug over 17 hours[29].

Furosemide, a famous "high ceiling" loop diuretic, suffers from a short half-life (1-2hrs) and short duration of action (~2hrs), besides a narrow absorption window. All these factors together provided a good rationale for its relatively low

bioavailability if administered in a repetitive regimen. Sustaining the release of the drug was hence a common goal to many researchers. Santus etal formulated a bioadhesive controlled release granules of the drug packed in hard gelatin capsules[30]. After an in vivo absorption study, Säkkinen etal concluded that microcrystalline chitosan granules containing furosemide could not be used as a gastroretentive drug delivery system in humans[31]. Recently Singhal etal developed multiparticulate floating microballons delivering the drug in a sustained pattern in the stomach[32].

Our present study deals with the development of a new gastroretentive sustained release formulation of furosemide. We investigated the possibility of designing a SPHC carrier device loaded with either furosemide alone or with a dosage form like a tablet or microspheres containing the drug.

Material:

Acrylamide (AM), potassium salt of 3-sulfopropylacrylate (SPAK), acrylic acid (AA), N, N'-methylenebisacrylamide (Bis), ammonium persulphate (APS), and N,N,N',N'-tetramethylethylenediamine (TEMED), all are products of Aldrich Chemical Company, USA).

Cross linked carboxymethylcellulose powder (Ac-Di-Sol®) (FMC Corp., Pennsylvania, USA).

Sodium bicarbonate (Adwic, el Nasr Pharmaceutical Co., Egypt).

Pluronic F127 (BASF Corporation, Chemical Division, Parsippany, NJ, USA).

Eudragit RSPO, Eudragit RLPO (Evonik Industries AG Rellinghauser Straße1-1145128 Essen, Germany).

Avicel PH 102 (FMC Biopolymers, FMC Corp., Pennsylvania, USA).

Magnesium stearate (Adwic, el Nasr Pharmaceutical Co., Egypt).

Furosemide was generously supplied by Memphis Pharmaceutical Co., Cairo, Egypt.

Methods:

-Preparation of the plain superporous hydrogel composite (SPHC):

Superporous hydrogels were generally synthesized by carrying out free-radical aqueous polymerization of acrylamide (AM) and potassium salt of 3-sulfopropylacrylate (SPAK) with acrylic acid (AA) in the presence of CO_2 gas bubbles. The gas bubbles were generated during the polymerization process due to the reaction between acrylic acid and sodium bicarbonate. Typically, the following components were added: a monomer (acrylamide (AM) + potassium salt of 3-sulfopropylacrylate (SPAK)), crosslinker (N, N'-methylenebisacrylamide (Bis)), deionized distilled water (DDW) (if necessary), foam stabilizer (Pluronic F127), acrylic acid, polymerization initiator (ammonium persulphate (APS)), initiation catalyst (N, N, N', N'-tetramethylethylenediamine (TEMED)), composite material (Ac-Di-Sol) and foaming agent (sodium bicarbonate). All the ingredients were added sequentially to a test tube (20 mm outer diameter x 150 mm in length). The test tube was shaken to mix the solution after each ingredient was added. The monomer solution was adjusted at pH 5. When sodium bicarbonate was added, the whole mixture was mechanically stirred instantaneously using thin spatula for several seconds to evenly distribute the generating gas bubbles. The ingredients and their amounts chosen for the preparation of the superporous hydrogel composite were based on preliminary studies and depicted in Table (1).

-Drug loading techniques:

The prepared SPHC was loaded with three different dosage forms of furosemide, namely: drug solution, previously formulated tablets and microspheres.

-Loading with drug solution (Soaked SPHC):

The prepared SPHC was loaded with furosemide by soaking in a buffer solution (pH 7.4) containing 40mg drug. Soaking was done for nearly two days in order to attain complete equilibrium. Formulation was filtered and the surface-adhered drug solution was removed by washing with buffer pH 7.4 and blotted with soft filter paper. Drying was performed in ambient air before storing in a 75% humidity chamber.

-Loading with furosemide tablets:

Furosemide matrix tablets were prepared using different concentrations of Eudragit RSPO and Eudragit RLPO, adopting the direct compression technique. In brief, the drug (40mg) and specific amounts of the polymer (Table 2) were mixed together, magnesium stearate (0.5%) was added and the whole mixture completed 100mg with Avicel PH 102. The best chosen formula was inserted inside the prepared SPHC by means of a central hole formed by making four incisions in the hydrogel from opposite sides with a fine scissor. The cut edge was then resealed (with a cyanoacrylate glue) to close again the formed hole after loading with the tablet.

-Loading with furosemide microspheres:

Microspheres were prepared by the solvent diffusion technique, using different ratios of Eudragit RSPO and Eudragit RLPO (Table 3). In brief, specific weights of the drug and polymer were dissolved in 10 ml ethanol. The solution was poured on 100 ml distilled water. The mixture was stirred till the complete evaporation of ethanol. The formed microspheres were filtered, washed with distilled water and air dried. The best chosen formula was filled in capsule no. (3), and placed inside the prepared SPHC by the same procedure as in the case of loading with tablets.

-Evaluation of the plain SPHC:

Plain SPHC was evaluated with respect to the swelling ratio, apparent density and floating behavior.

a. Swelling ratio:

The swelling behavior of the prepared SPHC was carried out by the teabag weight method[33], in which **0.100** g of the sample was added to a small bag made of nylon (50 mm x 90 mm; 200 mesh). The bag was completely immersed in the swelling medium [200ml simulated gastric fluid (SGF) (pH 1.2)] at room temperature for 24 hrs to reach the swelling equilibrium. Adhered liquid droplets on the surface of samples were removed by blotting with tissue paper. The swollen SPHC was weighed and then dried in an oven at 60 °C for ~ 6 hrs until there was no change in the weight of samples. The equilibrium swelling (ES) was defined as follows:$ES = \frac{(Ws-Wd)}{Wd}$

Where Ws and Wd are the respective weights of the swollen and dried SPHC.

b. Apparent Density:

The density of the dried SPHC was determined from the dry mass and volume measurements. The apparent density (d) was calculated by dividing the weight of a dried sample (W_d) by its volume (V_d). The volume (V_d) was calculated by a solvent displacement method[34]. Briefly, with the aid of forceps, a dried sample was immersed in a predetermined volume of hexane in a graduated cylinder. The increase in the hexane volume was measured as the volume of the dried sample.

C. Floating behavior:

The prepared SHPC was placed in a beaker containing 100ml simulated gastric fluid. The time taken by the prepared system to remain buoyant was considered as the total floating time. [35,15]

-Physical characterization of plain SPHC:

Scanning electron microscope:

The surface topography of plain SPHC was examined under an electron microscope (JSM- 6390LV, JEOL, Tokyo, Japan). A dry sample was transversely cut to expose the internal structure. The sample was added to a holder coated with gold palladium using sputter coater for one minute under argon gas.

-Evaluation of drug loading for soaked SPHC:

An accurately weighed amount (100 mg) of the dried loaded SPHC was continuously stirred in 250ml buffer pH 7.4 for 24 hrs. The solution was filtered; the volume completed again to 250ml with buffer system. The absorbance of the drug was determined spectrophotometrically at λ max 277 nm.

- Evaluation of tablets before insertion in SPHC:

All tablet formulae were prepared at a constant hardness of 6 kg. They were tested for weight variation, drug content uniformity, friability and dissolution. The weight variation and friability were determined according to the USP Pharmacopeial regulations. Dissolution was carried out in USP dissolution tester type II at a rotation speed of 100 rpm in 900 ml of simulated gastric fluid (SGF) (pH 1.2) for 24 hrs[36]. At regular time intervals, 3 ml samples of the dissolution medium were withdrawn and replaced with an equal volume of fresh media. The samples were analyzed for furosemide using a UV-Vis spectrophotometer (UV-1700, Shimadzu, Japan) at λ max 273 nm. All experiments were done in triplicate. The drug content uniformity was carried out by crushing a tablet and extracting 100 mg of the powder in 100 ml buffer pH 7.4. The solution was then passed through a 0.45 millipore filter and analyzed spectrophotometrically at λ max 277 nm. The test was done in triplicate.

-Evaluation of microspheres before insertion in SPHC:

An accurate weight of each of the prepared microsphere formulae equivalent to 40 mg drug was dissolved in 10ml alcohol. The solution was then added to 50 ml buffer solution (pH 7.4) and placed on a stirrer till the complete evaporation of alcohol. The solution was filtered, adjusted to 50 ml, and measured spectrophotometrically at λ max 277 nm. Encapsulation efficiency percent was then calculated by the following equation:

$$\text{Encapsulation efficiency} = \frac{\text{actual amount of drug loaded}}{\text{theoretical amount}} \times 100$$ [37]

Release of furosemide from the prepared microspheres was tested in a USP dissolution tester type II as mentioned under the evaluation of tablets.

-In-vitro furosemide release study from the prepared formulae:

The in-vitro drug release was carried out by filling the calculated amount of loaded SPHC in capsule shell (size 000), using a USP dissolution test apparatus type II at a rotation speed of 100 rpm in 900 ml of simulated gastric fluid (SGF) (pH1.2) for 24 hrs[36]. At regular time intervals, 3 ml samples of the dissolution medium were withdrawn and replaced with an equal volume of fresh media. The samples were analyzed for the drug using a UV-Vis spectrophotometer (UV-1700, Shimadzu, Japan) at λ max 273 nm. All experiments were done in triplicate.

-Kinetic treatment of the released data:

The release data were treated statistically according to linear regression analysis. The data were fitted to zero order, first order and Higushi diffusion model.

Results and Discussion:

Evaluation of plain SPHC:

The prepared SPHC exhibited an equilibrium swelling (ES) of 15.63 (fig: (1)). The calculated apparent density was 0.56 g/cm^3, which proposed a light and porous structure. Scanning electron micrographs (fig :(2)) of plain SPHC assisted the previous results, where a highly interconnected porous matrix was clearly shown.

SPHC remained buoyant in simulated gastric fluid for 24 hrs, suggesting its suitability as a controlled release drug delivery device in the stomach.

Fig (1): Photographs of superporous hydrogel composite before (a) and after (b) swelling.

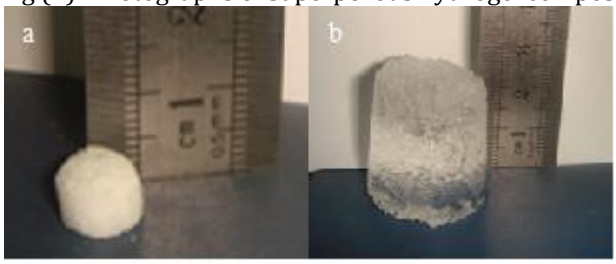


Fig (2): Scanning electron micrograph of superporous hydrogel composite.

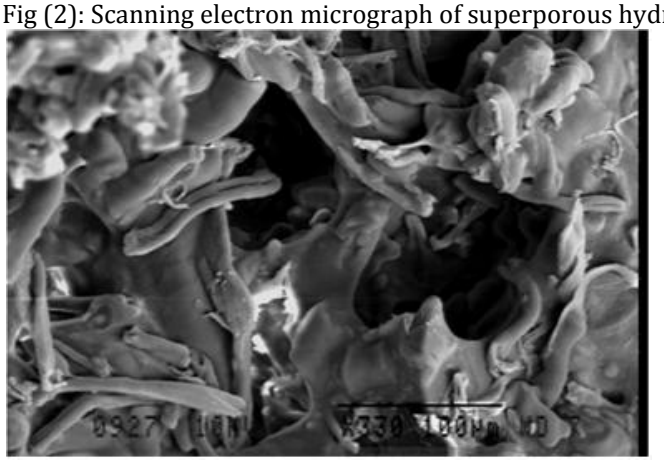


Table (1): Composition of Superporous Hydrogel Composite:

Monomer Type	Monomer weight (µl)	Crosslinker (2.5 % Bis) (µl)	Foam Stabilizer (10 % PF 127) (µl)	Acid (µl)	Initiator (20%APS (µl)	Composite Material (Ac-Di-Sol®) (mg)	Initiation Catalyst (20% TEMED) (µl)	Foaming Agent ($NaHCO_3$) (mg)
AM + SPAK	1200 (50% AM)+ 900 (50% SPAK)	450	90	30 (AA)	45	270	45	100

-Evaluation of loaded SPHC:

Results for ES, apparent density and floating time remained constant after loading with either solution, tablets or microspheres of furosemide.

SPHC soaked in a drug solution gave a drug loading equivalent to100 ug/mg SPHC.

-Evaluation of tablets before insertion in SPHC:

All results for quality control tests of prepared tablet formulae (Table (2)) complied with Pharmacopeial regulations.

-Release profile of furosemide from tablet formulae:

Comparing the behavior of the two tested polymers in tablet formulae showed that: Eudragit RSPO gave a drug release rate constant; that is 38% and 32% lower than Eudragit RLPO at 1:0.25 and 1:0.5 drug: polymer ratios, respectively (Figure (3)). Since Eudragit RSPO was more efficient than its analogue in retarding the release of furosemide at the two tested ratios by a similar percent, the tablet formula with lower content of polymer (1:0.25) was chosen for insertion in SPHC.

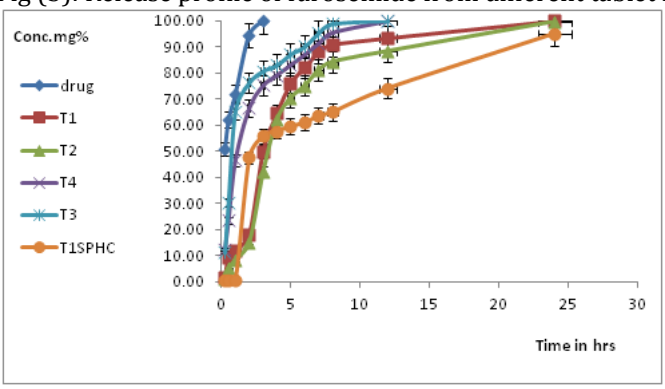
Table (2): Evaluation of furosemide tablets

Formulae			Drug content (mg)±SD*	Hardness (kg)	Friability (%)	Weight variation (mg) ±SD*
No	D:P**	Polymer Type				
T1	1:0.25	Eudragit RSPO	40 ± 1.60*	Constant in all formulae	<1% in all formulae	99.9 ± 2.3*
T2	1:0.5	Eudragit RSPO	40 ± 1.54*			100.23 ± 0.46*
T3	1:0.25	Eudragit RLPO	40 ± 1.68*			100.57 ± 1.59*
T4	1:0.5	Eudragit RLPO	40 ± 0.96*			101.6 ± 1.67*

SD*: standard deviation

D:P**: drug to polymer ratio

Fig (3): Release profile of furosemide from different tablet formulae and SPHC loaded with selected tablet formulae.



-Release profile of furosemide from SPHC loaded with the selected tablet formula:

While the tablet formula T1 exhibited a drug release rate equivalent to a $t^{1/2}$ of 2.5 hrs, insertion of T1 inside SPHC caused a retardation in release equivalent to a $t^{1/2}$ = 6 hrs. This result could be explained by the fact that much of the dissolution medium diffusing inside the SPHC was lost on the expense of the swelling process. The remaining free volume available for the access of tablet was not sufficient to disintegrate its matrix. Alternatively, gradual erosion of tablet might cause slow drug release to occur. Furthermore, the drug released from the tablet had to diffuse through numerous tortuous channels and pores in order to be finally delivered outside the SPHC.

-Evaluation of microspheres before insertion in SPHC:

All prepared microspheres showed nearly maximum percent encapsulation efficiency (Table (3)). Such result could illustrate the success of the solvent diffusion technique in entrapping furosemide inside the matrix of Eudragit polymers[38]

-Release profile of furosemide from prepared microspheres:

Increasing polymer content (Eudragit RSPO) from one third (M2) to one half (M1) of drug included in microspheres did not significantly affect the drug release rate where a similar k value of 8.6781 and 8.6674 mg/hr was obtained for M2 and M1, respectively (Table (4)). A similarity in rate also prevailed with Eudragit RLPO microspheres at the same drug to polymer ratios, namely, 3:1 (M4) and 2:1 (M3), respectively
(Figure (4)). However, a slight higher release rate than that encountered in Eudragit RSPO microspheres was shown at both tested ratios. Besides, a shift in the mechanism of drug release from zero-order (M1, M2) to diffusion model (M3, M4) was identified (Table (4)). This result seemed in agreement with other research articles[39] that interpreted the higher diffusion controlled release rate of Eudragit RLPO to higher porosity and wider network structure of the polymeric backbone.

Table (3): Evaluation of furosemide microspheres

Formulae			Encapsulation efficiency (%)±SD*
N0	D:P**	Eudragit Type	
M1	2:1	RSPO	98 ± 1.24*
M2	3:1	RSPO	101 ± 1.43*
M3	2:1	RLPO	99 ± 1.98*
M4	3:1	RLPO	100 ± 1.96*

SD*: standard deviation

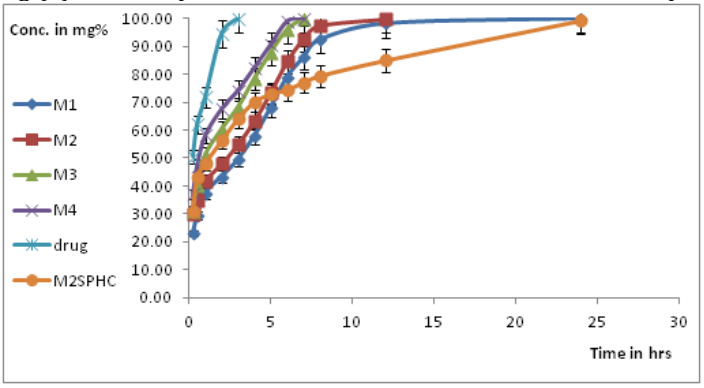
D:P**: drug to polymer ratio

Table (4): Kinetic treatment of furosemide release data from different formulae

Formula Code	Order	K*	$t^{1/2}$**	Y intercept	
				Value	Significance
drug	diffusion	41.335	0.668	31.529	31.529•
Soaked	first	-1.386	0.5	1.4426	3.609•
T1	first	-0.267	2.5	2.0177	……..••
T2	first	-0.234	3	2.0445	……..••
T3	first	-0.437	1.6	1.9035	1.249•
T4	first	-0.339	2	1.9122	1.224•
T1 SPHG	first	-0.117	6	1.9262	1.185•
M1	zero	8.6674	2.9	24.698	24.698•
M2	zero	8.6781	2.3	30.187	30.187•
M3	diffusion	31.565	1.03	16.601	16.601•
M4	diffusion	29.377	0.92	25.22	25.22•
M2SPHG	diffusion	17.778	1.06	29.858	29.858•

• flush release in mg%
•• absence of flush release
**k for first order in hr^{-1}*
**k for zero in mg/hr*
**K for diffusion in $mg/hr^{1/2}$*
*** $t^{1/2}$ in hrs*

Fig (4): Release profile of furosemide from different microspheres and SPHC loaded with selected microspheres formula.



-Comparison of furosemide release profile with the selected microspheres formula before and after loading with SPHC:

Microspheres formula (M2) with lower content of Eudragit RSPO was inserted in SPHC. Kinetics of drug release was compared to that of free M2 before insertion as well as for the free drug. Table (4) showed similar values of flush release for M2, M2SPHC and free drug. This indicated equal affinity for dissolution medium to either wet the free drug and/or diffuse into both systems. For the subsequent time intervals, furosemide release from microspheres (M2) proceeded at a lower rate (k= 8.6781mg/hr) than that of powder drug alone (k=41.335 $mg/hr^{1/2}$). This result could be interpreted by the low permeability of Eudragit RSPO matrix structure forming the microspheres. Surprisingly, the inclusion of M2 in SPHC caused an increase in the drug release rate corresponding to a $t^{1/2}$=1.06 hrs relative to $t^{1/2}$= 2.3 hrs in case of M2 (before insertion in SPHC). This unexpected result could be believed to occur on two stages. First, a rapid inward diffusion of the dissolution medium caused a rupture in the gelatin capsule shell with subsequent propagation of included microspheres

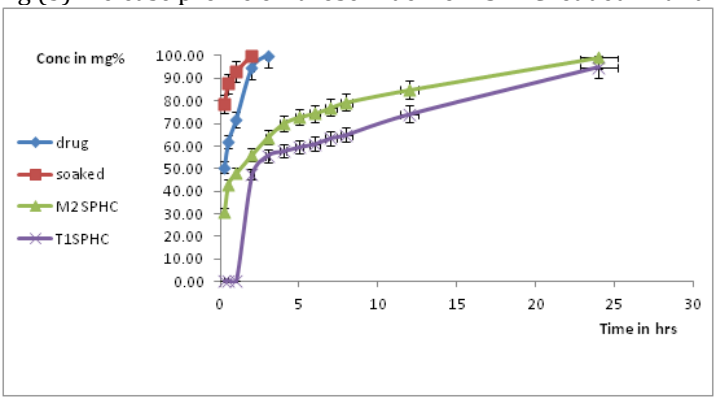
within SPHC matrix. Second, an excessive swelling of SPHC occurred by further penetration of dissolution medium as shown in Figure (1).The increase in volume accompanying the swelling process might exert some sort of environmental pressure on the microspheres present within the swollen matrix. Being non plasticized, the polymeric film of Eudragit RSPO might lose its integrity as a result of the applied stress, with probable formation of surface cracks and fissures. Drug release was thus enabled at a much higher rate.

-Comparison of furosemide release profile from different SPHC loaded formulae:

As shown in Table (4) and Figure (5), the release half-life for furosemide was very similar before and after soaking in SPHC. However, a significant diminution of flush release occurred for the soaked SPHC (3.6 relative to 31.5 mg% in case of free drug). This could be reasonable since the drug was present in the form of solution inside the soaked SPHC and no initial wetting was required. Hence, the rate limiting step for outward drug release was the time taken to pass through the tortuous channels and pores of the swollen hydrogel matrix.

Release kinetics for T1SPHC revealed a combined effect of low flush equivalent to ~ 1.2 mg% and an extended release rate equivalent to a $t^{1/2}$ = 6 hrs, suggesting tablet to be a successful dosage form controlling drug release within SPHC matrix. On the contrary, M2SPHC showed both high initial flush (~ 29.9 mg %) and a high rate of drug release equivalent to a $t^{1/2}$ = 1.06 hrs, which led to interpret the unsuitability of the multiparticulate dosage form as a tool for controlling drug release inside SPHC.

Fig (5): Release profile of furosemide from SPHC loaded with different formulae.



CONCLUSION

Successful drug loading could be achieved within the matrix of SPHC. However, the applicability of the superporous hydrogel system as a controlled release, gastroretentive device largely depended on the type of dosage form included. Tablets as an example of solid unit dosage form proved to be much superior to either multiparticulate solid systems or simply the loaded drug solution.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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