Effect of modification of formulation variables on physical characterization of superporouse hydrogel

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Abstract:

Superporouse hydrogel (SPH) is widely used and investigated as a gastro retentive drug delivery system to extend drug residence time in the stomach

However, their mechanical strength represents a problem because they need to withstand the peristaltic movement of the stomach. Properties of SPH are widely affected by the materials used for their synthesis. The aim of the research is to study the effect of changing the foaming agent and foam stabilizer amount on physical properties, in particular mechanical strength, and drug release from SPH. Trifluoperazine HCl will be used as model drug in the study.

SPH formulations was prepared using fixed amount of acrylamide (AM) and polyvinyl alcohol (PVA) as monomers, polyethylene glycol diacrylate (PEGDA) as cross-linker, TRFP as model drug and variable amount of sodium bicarbonate ($NaHCO_3$) as foaming agent, and tween 20 as foam stabilizer. Ammonium persulphate (APS) / tetramethyl ethylenediamine (TEMED) system was used as polymerization initiator. The effect of changing foaming agent and foam stabilizer on mechanical strength, buoyancy, porosity, density, drug release, drug content, swelling ratio, and swelling time was investigated.

Modifying both factors affected all the physical properties and drug release profile. When tween 20 was increased the mechanical strength, density and floating lag time was increased with a reduction in porosity and drug release. While increasing $NaHCO_3$ reduced mechanical strength, density and floating lag time with increased porosity and faster drug release was observed. Optimum physical properties were observed in formula 2 which had 230 µl of Tween 20 (v/v) and 50 mg of $NaHCO_3$ in which the mechanical strength was 579±0.4, floating lag time 14 min and 80% of the drug was released within 12 hr.

As a conclusion SPH with improved mechanical strength, physical properties and drug release pattern can be achieved by changing foam stabilizer and foaming agent amount in the formulations.

Keywords: Monomer, Cross-linker, Superporous hydrogel (SPH), foaming agent and composite agent. Acryl amide (AM), Trifluoperazine HCl (TRFP), Poly vinyl alcohol (PVA), Super porous hydrogel composite (SPHC), Methylene-Bis-Acrylamide (MBA).

تأثير تعديل متغيرات الصياغة على التوصيف الفيزيائي لهيدروجيل فائق المسام

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الخلاصة:

Superporouse Hydrogelيستخدم على نطاق واسع ويتم فحصه كنظام لتوصيل الأدوية المعوية لإطالة وقت بقاء الدواء في المعدة. ومع ذلك، فإن قوتهم الميكانيكية تمثل مشكلة لأنهم بحاجة إلى تحمل الحركة التمعجية للمعدة. (SPH) على نطاق واسع بالمواد المستخدمة في تركيبها. الهدف من البحث هو دراسة تأثير تغيير كمية عامل الرغوة وكمية تتأثر مثبت الرغوة على الخصائص الفيزيائية، وخاصة القوة الميكانيكية، وإطلاق الدواء من الجل وذلك بأستخدام دواء Trifluoperazine HCl كدواء دوائي

تم تحضير تركيبات الجل من كحول البولي فينيل كمونومرات (PVA) باستخدام كمية ثابتة من مادة الأكريلاميد (AM) بأستخدام دواء نموذجي بيكربونات TRFP ، و (PEGDA) كوصلة متقاطعة وثنائي أكريلات البولي إيثيلين جليكول كعامل رغوة, تم استخدام نظام (TEMED)/ (APSكبادئ بلمرة، و توين ٢٠ كمثبت للرغوة, ((NaHCO3 الصوديوم كعامل ارغاء. تم دراسة تأثير تغيير عامل الرغوة ومثبت الرغوة على القوة الميكانيكية، والطفو، والمسامية، والكثافة، وإطلاق الدواء، ومحتوى الدواء، ونسبة الانتفاخ، ووقت الانتفاخ

أثر تعديل كلا العاملين على جميع الخصائص الفيزيائية وملف إطلاق الدواء. عندما تمت زيادة توين ٢٠، زادت القوة القوة الميكانيكية، عامل الميكانيكية والكثافة ووقت التأخر العائم مع انخفاض في المسامية وإطلاق الدواء. في حين أن زيادة الرغوة لوحظت الكثافة ووقت التأخر العائم مع زيادة المسامية وإطلاق الدواء بشكل أسرع. لوحظت الخصائص الفيزيائية حيث NaHCO3 (حجم / حجم) و ٥٠ مجم من Tween 20 المثلى في الصيغة ٢ التي تحتوي على ٢٣٠ ميكرو لتر من .كانت القوة الميكانيكية ٥٧٩ ± ٠,٤، وقت التأخر العائم ١٤ دقيقة و ٨٠٪ من الدواء تم إطلاقه خلال ١٢ ساعة

مع قوة ميكانيكية محسنة وخصائص فيزيائية ونمط إطلاق الدواء عن طريق تغيير مثبت SPH كخلاصة يمكن تحقيق الرغوة وكمية عامل الرغوة في التركيبات.

الكلمات المفتاحية: مونومر ، رابط متقاطع ، هيدروجيل فائق المسام ، عامل رغوة وعامل مركب. أكريل أميد ، بولي فينيل كحول ، مركب هيدروجيل مسامي فائق ، ميثيلين-بيس-أكريلاميد.

Introduction

A gastroretentive drug delivery system (GRDDS) is an approach widely used and investigated in oral drug delivery to maintain the medication in the stomach for an extended period of time (1). It is specifically advantageous for drugs with narrow absorption windows, drugs that are highly absorbed from the stomach, or drugs intended for local gastric effect (2). The floating system, mucoadhesive system, swellable, magnetic system, high-density sinking system, expandable, unfoldable system, and super porous hydrogel (SPH) are some of the various methods of gastro retentive drug delivery that is being developed, and of special interest is SPH (3,4).

SPH is a three-dimensional non-soluble hydrophilic polymeric network that quickly absorbs large amounts of water and expands in size to a hundred times its original weight without dissolving (5). Their large size and floating properties allow in addition to their biocompatibility, stability at the stomach's acid environment and mechanical strength to be used as GRDDS. Polymers widely utilized are either synthetic such as polyacrylamide, poly (acrylic acid), polyvinyl alcohol (PVA), and polyvinyl pyrrolidone (PVP), or natural (such as chitosan, alginate, gelatin, and carboxymethyl cellulose) (6,7).

SPH physical properties are widely affected by the type and concentration of polymers and crosslinkers used in addition to formulation conditions. For example, it was reported that the release of baclofen was prolonged when prepared as SPH (8). The aim of our work is to study the effect of modification of formulation variables on the physical properties and drug release kinetics of SPH using trifluoperazine HCl (TRFP) as a model drug and polyethylene glycol diacrylate as a high molecular weight crosslinker. TRFP is used because

of its fast absorption from the stomach, used twice or three times a day based on the indication and has low dose that is suitable for SPH because low doses are required for this form.

Experimental Work

Materials

Triflouperazine HCl (TRFP) (AV global corporation-India), acrylamide (AM) (CDH-India), tween 20 (Alpha chemical-India), polyvinyl alcohol (PVA) (Panreac-Spain), polyethylene glycol diacrylate (PEGDA), sodium bicarbonate, tetramethyl ethylenediamine (TEMED) (HIMEDIA-India), ammonium persulphate (APS) (THOMAS BAKER-India)

Super Porous Hydrogel Composite Preparation

The gas blowing method was employed for the preparation of TRFP as super porous hydrogel composite (SPHC). (AM) as monomer, high molecular weight poly (ethylene glycol) diacrylate (PEGDA) systems (700 Da) as crosslinker and poly vinyl alcohol PVA as composite agent were used. As foam stabilizing agent tween 20 was used while ammonium persulfate (APS)/ tetramethyl ethylenediamine TEMED both was used as polymerization initiator pair. Sodium bicarbonate was used as gas generating or foaming agent. The required amount of each ingredient is demonstrated in table (1).

First, the required amount of PVA was weighed and placed in a glass test tube of (10 ml in volume). Then a stock solution of AM (40% w/v) and APS (20% w/v) in distill water were prepared and 300 µl of the stock solution of AM was added to PVA followed by the required amount of tween 20 (v/v). The mixture was sonicated for 5 minutes at 50°C. After sonication 3 mg w/w of TRFP was weighed and added to the test tube followed by 45 µl of the stock solution of APS & mixed thoroughly using vortex mixer for few seconds followed by the addition of 45 µl of TEMED (20% v/v). Immediately after the addition of APS, the required amount of sodium bicarbonate was added and the final formula left to stand for 15 min to complete the polymerization process. After that the SPHC was removed from the test tube carefully using forceps and left to dry for 72 hours at room temperature (9)

Table (1): Formulas of SPH

Formula/ Active ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
AM 40% (µl)	300	300	300	300	300	300	300	300	300
PVA (mg)	20	20	20	20	20	20	20	20	20
Tween 20 (µl)	200	230	260	290	320	200	200	200	200
PEGDA (µl)	4	4	4	4	4	4	4	4	4
TRFP (mg)	3	3	3	3	3	3	3	3	3
APS 20% (µl)	45	45	45	45	45	45	45	45	45
TEMED 20% (µl)	45	45	45	45	45	45	45	45	45
$NaHCO_3$ (mg)	50	50	50	50	50	70	90	110	130

Characterization of the prepared SPHC

Density measurement

A solvent displacement approach was used to measure density. A dry sample of SPH was weighed (W_{SPH}), and it was then submerged in a set amount of n-hexane in a graduated cylinder. The increase in n-hexane volume was used to calculate the SPHC volume (V_{SPH}). The following equation was used to compute density (10).

$$\text{Density} = W_{SPH} / V_{SPH} \quad \ldots\ldots (1)$$

Porosity measurement

Dry hydrogel was weighed (M1) and submerged in ethanol for 12 hours to evaluate porosity. Then the hydrogel was removed from ethanol and extra fluid was plotted using filter paper and weighed (M2). The porosity was estimated using the equation below (10).

$$\text{Porosity} = (M_2 - M_1) / PV \ldots\ldots (2)$$

Where P = density of ethanol and V = initial hydrogel volume.

Swelling ratio measurement

Measurement of the swelling ratio was done using the gravimetric method (Qs). The dried SPHC was weighed (Wd), added to the swelling medium, and removed after a set amount of time, blotted using filter paper to remove extra fluid and weighed (Ws). The swelling medium used was 0.1N HCl. The Q_s was calculated using the following equation:

$$Q_s = [(W_s - Wd) / Wd] * 100 \ldots\ldots (3)$$

Time to reach maximum swelling was determined as the time in which no change in swelling ratio was observed and the hydrogel reached constant weight (11).

Floating study

Each formula's dried hydrogel was put in a beaker with 100 ml of 0.1N HCl, and the amount of time it took for SPHC to float was known as the floating lag time, while the amount of time it took for SPH to stay buoyant was known as the total floating time (12).

***In-vitro* drug release**

The dissolution device (USP type II) was used in 900 ml of 0.1N HCl at 100 rpm paddle speed for 12 hours at 37.5°C during the in-vitro drug release test for SPHC. A 5ml sample of the dissolution medium was taken out and replaced with an equal volume of the fresh medium solution at predetermined intervals. A UV spectrophotometer (Shimadzu, Japan) was used to analyze each sample's absorbance, and the percentage of medicine release was calculated (12).

Drug release kinetics

The *in vitro* release data were fitted to a variety of mathematical kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models and their equations presented in table (2). The formula release kinetic model with the highest regression coefficient R^2 after analyzing each formula was selected (13).

Table (2): Mathematical equations for Drug release kinetics

Mathematical model	Equation	Interpretation of symbols
Zero Order model	$M_t = M_0 + K_0 t$	M_t = the amount of drug dissolved in time t. M_0 = the initial amount of drug in solution which is often zero. K_0 = the zero-order release constant.
First Order model	$\text{Log } M_t = \log M_0 - K_1 t/2.303$	M_t = the amount of drug released in time t. M_0 = the initial amount of drug in the dosage form K_1 = the first order release constant.
Higuchi Model	$M_t = K_H (t)^{0.5}$	M_t amount of drug release at time t, K_H = the Higuchi diffusion constant
Korsmeyer-Peppas Model	$q = M_t / M_\infty = k_{KP} . t^n$	$q = M_t/M_\infty$ is the fraction of drug released at time t k_{KP} is the release rate constant, n is the diffusion exponent, which indicates the type of drug transport mechanism through the polymer

The type of drug release mechanism was identified based on the diffusion exponent value (n) derived from the Korsmeyer-Peppas model. Fickian diffusion happens when (n) is less than 0.5, anomalous (non-Fickian) diffusion occurs when (n) is between 0.5 and 1, Case-II transport (erosion) occurs when (n) equals 1, and Super case-II transport occurs when (n) is larger than 1(13).

Drug content determination

For each formulation a sample of dry SPHC containing 3mg TRFP was placed in a volumetric flask with a 100 ml 0.1N HCl (pH 1.2) and stirred with magnetic stirrer for 24 hr. The amount of TRFP in the tested formula was then estimated after the absorbance was measured using a UV spectrophotometer at the proper lambda max (λ_{max}= 255) (11,14).

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy FTIR was used for the formulas to examine the possibility of chemical bond formation during polymerization between the drug and the composition of the formula. The pure drug, formula without drug and formula with the drug were examined. The samples were analyzed using Bruker FTIR (Shimadzu, Japan) with Attenuated Total Reflectance (ATR) technology. FTIR spectra scanning between 400 cm^{-1} and 4000 cm^{-1} was used (15–18).

Variables studied in formulation

Variation in foam stabilizing agent (Tween 20) and foaming agent ($NaHCO_3$) amount in each formulation were studied regarding their effect on physical properties, swelling properties, drug release and release kinetics of TRFP in SPHC.

Statistical analysis

All data were reported using a mean standard deviation format. Using the SPSS20 software program, the analysis of variance (ANOVA) test was conducted to compare the differences between different groups. The lowest level of statistical significance was regarded a significance level ($p<0.05$) (15).

Results and Discussion

Superporous hydrogel composite (SPHC)

All the formulas were successfully prepared by free radical polymerization. SPHC was created by the polymerization of monomers while they were surrounded by gas bubbles. After initiating radical polymerization in the polymerization step with a mixture of APS/TEMED redox pair, the monomers will join covalently and cross-link with PEGDA to produce extended chains. Tween 20 will act as a stabilizer for the carbon dioxide gas bubbles produced by the reaction of $NaHCO_3$ with the substance during the foaming process (19). The properties of SPHC are affected by the compositions of the formulation. A study on the effect of composition amount on the characteristics of SPHC was conducted.

Effect of the amount of Tween 20 as a foam stabilizing agent

In this work, Tween 20 was utilized as a foam stabilizing agent to stabilize the foaming process and regulate the amount of gas bubbles produced. As the gas bubbles are controlled, preserved, and uniformly distributed, the internal structure of the SPHC will become less random and enhanced due to the uniform distribution of the intercellular capillary channel network, which is necessary for good swelling, and this will result in an increase in the viscosity of the monomers used in the formulation process and enhancing the swelling properties (20).

Based on the aforementioned information, the formulas F1, F2, F3, F4, and F5 were formulated to contain Tween 20 in amounts of (200, 230, 260, 290, and 320 µl) and the results are displayed in table (3) demonstrates that a decrease in porosity and an increase in density led to a drop in the swelling ratio was observed. It will be enhanced due to the homogeneous distribution of gas bubbles, which will result in a uniform intercellular capillary network with rapid swelling (less swelling time) and a reduced swelling ratio. The decrease in porosity will reduce the time required for fluid to enter the hydrogel matrix and as a consequence will increase floating lag time. The results in table 3 demonstrated increase in mechanical strength due to increase in density as a results of uniform void distribution. In 2021 Jaleel and Jawad also reported that increasing the amount of foaming agent in formulations resulted in decrease in porosity and swelling ratio with an increase in density and mechanical strength (8). Dhingra et al formulated different SPHs for loratadine and they reported that when the density of the hydrogels prepared reduced, the mechanical strength will be reduced in addition to reduction in swelling ratio (7). Drug contents for all formulas (F1, F2, F3, F4, F5) were in the acceptable limits indicating no drug lose within and after the formulation process of the SPHC.

Table (3): Effect of the different amount of Tween 20 as a foam stabilizing agent

Formula No.	Density g/cm^3	Swelling Time (hr.)	Swelling Ratio	Mechanical strength g	Porosity	Floating Lag time (min)	Floating Time (hr.)	Drug Content (%)
F1	0.931± 0.015	11	3.8±0.21	558±2.8	0.0836±0.003	12±1	24	99.9%
F2	0.931±0.008	9	3.7±0.16	579±1.04	0.0836±0.003	14±1	24	98.2%
F3	0.961±0.02	9	3.5±0.35	627.8±2.5	0.0736±0.001	16±1	24	99.9%
F4	0.974±0.009	8	3.4±0.3	641±5.4	0.061±0.003	17±1.5	24	99.9%
F5	0.976±0.005	7	2.7±0.009	665±18.3	0.058± 0.003	18±0.5	24	101.5%

Drug release was studied and the results demonstrated in figure 1. Increasing foam stabilizer amount slows TRFP release. The number of CO_2 bubbles was uniformly distributed, leading to a uniform interconnecting chain capillary structure of the SPHC, that make the formula denser and more rigid which result in less void of fraction and slower media enter the channels of the SPHC. Also, the decrease in porosity and swelling ratio observed led to a slow release of the entrapped drug.

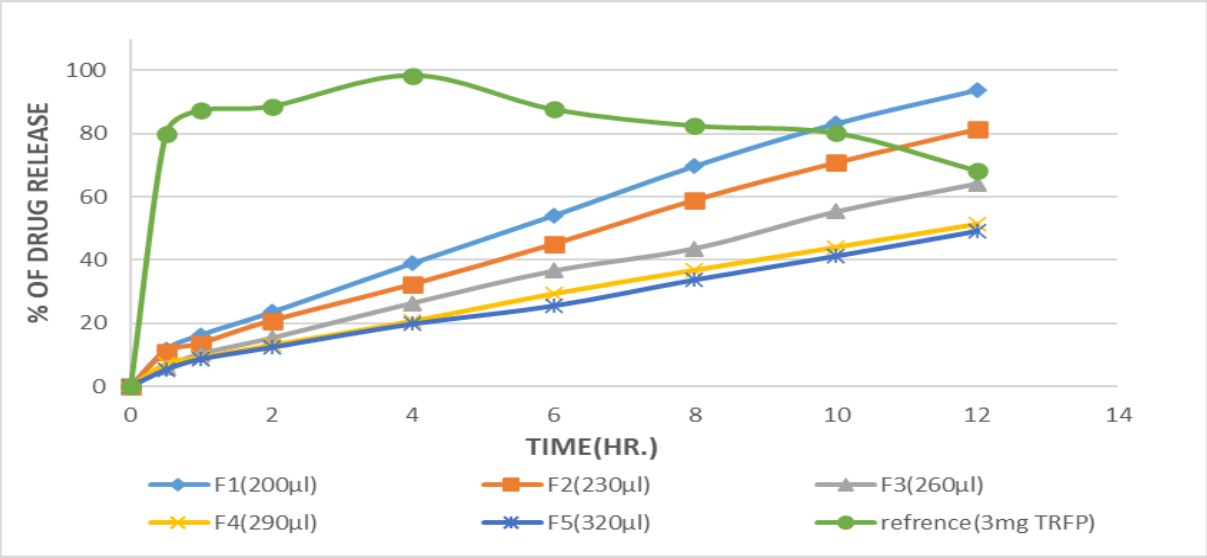

Figure (1): The effect of different amount of the Tween 20 as a foam stabilizing agent on the release profile of formulas (F1-F5)

Effect of foaming agent amount

An increase in the foaming agent $NaHCO_3$ will have an effect on the physical properties of the prepared SPHC. Higher foaming agent will result in the generation of more CO_2 bubbles, large number of pores and well interconnected inner network. The results in table (4)

demonstrated that effect. The porosity increased with increasing $NaHCO_3$ which in turn reduced the density and mechanical strength of the formulations. As more voids are created within the SPHC, the porosity will grow, the density will decrease, and the structure of the SPHC will become more brittle, allowing the gastric media to diffuse more quickly. The quick diffusion resulted in a reduction in floating lag time and overall swelling time. The swelling ration was slightly reduced from F1 to F14 and F15 then increased in F16 and F17. This could be explained that the network reached maximum stretching due to uniform distribution of pores created by high amount of CO_2 bubbles and no more swelling can be achieved. Similar findings were reported by Ghazali and Adnan. They studied the effect of foaming agent on swelling and noticed that increasing sodium bicarbonate to 0.4wt% resulted in an increase in water absorption and swelling ratio. However, increasing above 0.4wt% resulted in a decrease in swelling behavior (21). Drug content was uniform and within the acceptable limits (22,23)

Table (4): Foaming agent amount impact on SPH properties

Formula No.	Density g/cm^3	Swelling Time (hr.)	Swelling Ratio	Porosity	Floating Lag time (min)	Mechanical strength g	Floating Time (hr.)	Drug Content (%)
F1	0.936± 0.01	11	3.8±0.21	0.05± 0.002	12	**558±2.8**	24	99.9%
F6	0.93± 0.004	10	2.8±0.44	0.103± 0.02	11	**466±5.2**	24	99.8%
F7	0.929± 0.005	7	3.5±0.75	0.111± 0.04	12	**351.3±8**	24	100.1%
F8	0.927± 0.008	7	3.8±0.24	0.115± 0.02	11	**259±5**	24	99.9%
F9	0.913± 0.01	7	3.8±0.71	0.118± 0.02	10	**158±6**	24	101.5%

Figure (2) reveals that the percent of drug release for formulas F1-(F6-F9) reaches approximately 50 percent in the first 6 hours and reaches its maximum after only 12 hours. This relatively rapid drug release was attributed to the increased amount of the foaming agent $NaHCO_3$, which results in increased porosity, allowing a greater amount of the dissolution media to penetrate the interconnected pores as in previously reported (24). El-said et al reported that the release of baclofen was extended compared with commercial tablet. The commercial tablet release 80% of the drug within half an hour while SPHH formulation released 80% of the drug within 6 hrs. and the less porous structure extended the release of the drug (25).

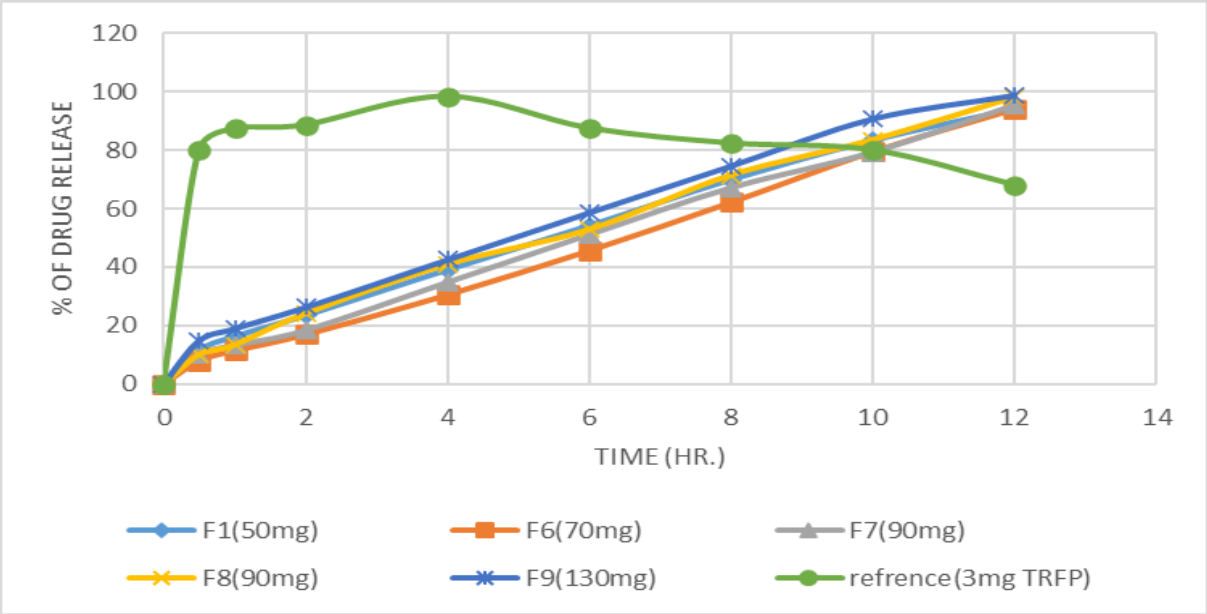

Figure (2): The effect of the foaming agent ($NaHCO_3$) on the percent of the model drug release for formulas (F1, F6-F9)

Mathematical model of drug release

As noticed in table (5) all formulations followed zero order kinetics except F4 which followed first order kinetics. The values of R^2 (regression coefficient) for each formula and in different mathematical models of the drug release in 0.1N HCl solution are illustrated as follow:

Table (5): Mathematical Models Correlation Coefficient Values

	Zero order		First order		Higuchi		Korsmeyer-peppas		
	$K_0(hr^{-1})$	R^2	$K_1(hr^{-1})$	R^2	$K_H(hr.)^{1/2}$	R^2	$K_{KP}(hr.)^{-n}$	R^2	n
F1	7.5799	0.9909	0.209	0.92	0.5466	0.9737	29.23	0.9904	1.4659
F2	6.4591	0.9922	0.129	0.9657	0.5	0.9821	31.94	0.9827	1.5044
F3	5.1308	0.9929	0.080	0.987	0.462	0.9678	23.29	0.9971	1.3673
F4	4.0326	0.9911	0.055	0.9952	0.3905	0.982	34.64	0.9827	1.5396
F5	3.8457	0.9925	0.051	0.9895	0.3903	0.9779	28.35	0.993	1.4526
F6	7.6459	0.9975	0.207	0.862	0.6003	0.9902	17.40	0.9824	1.2406
F7	7.6694	0.9965	0.218	0.8584	0.579	0.9826	21.48	0.9777	1.3322
F8	7.8932	0.9931	0.270	0.8122	0.5771	0.9674	22.41	0.9932	1.3505
F9	7.9878	0.9878	0.211	0.914	0.5435	0.9781	37.10	0.9823	1.5694

The equations of the mathematical models of the release kinetics that listed previously in table (2) were applied to the values of the percent of drug release for all formulas, and the results indicated that: the super porous hydrogel composite formulas were determined by fitting all formulas to the zero-order kinetics and Higuchi models, as shown in table (5).

ATR-FTIR

Since polymerization process took place in the presence of the drug it was essential to examine if the drug was affected by the

process and Bruker FTIR (Shimadzu, Japan) with Attenuated Total Reflectance (ATR) technology was used. The FTIR spectra of the pure drug, formula with drug and formula without drug were examined. As seen in figure (3), the drug's peaks can be seen in the SPHC spectrum, indicating that there is no chemical incompatibility between the medication and the polymer

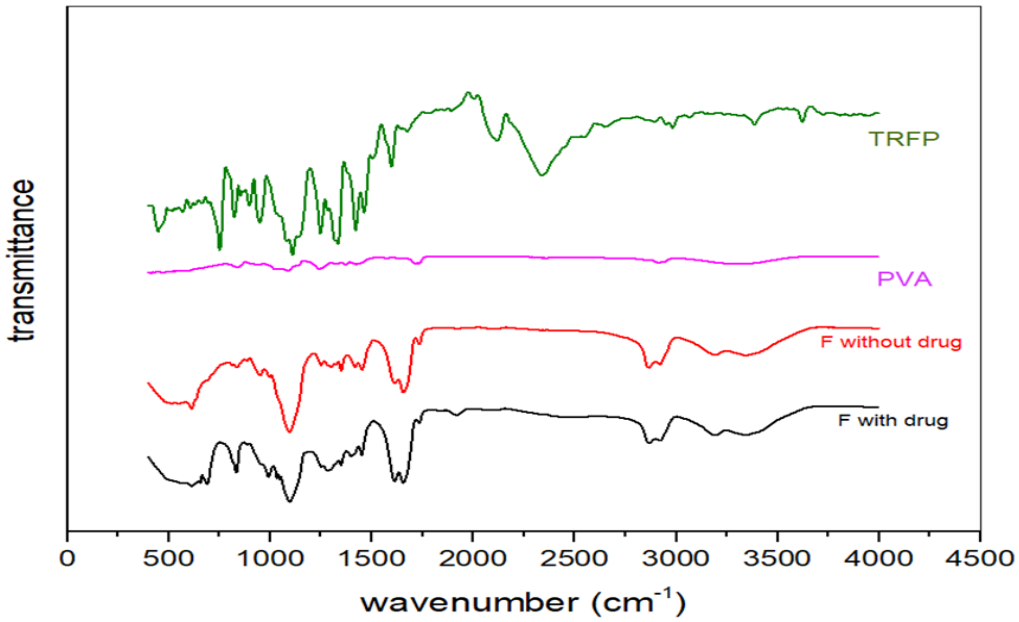

Figure (3): ATR-FTIR of (a)TRFP (b)PVA (c)formula with drug (d) formula without drug

Selection of the optimum formula

For a SPHC to work as GRDDS the gel should quickly swell to a large size and float for a long period in the stomach. Also, it should have a mechanical strength to withstand the peristaltic movement of the stomach and slow the release of the drug for a once daily application. Based on the above criteria all formulations were compared regarding their physical properties and F9 was chosen as the optimum formula because of low floating lag time (10 min), time to reach maximum swelling (7 hr), and high swelling ratio (3.8) , 24 hour floating time , drug content 101.5% and complete drug release within 12 hr. following zero order kinetics (12).

Conclusion

SPHC was successfully prepared using gas blowing technique and free radical polymerization. Changing the formulation factors affected all the physical properties such as swelling ratio, floating lag time, density and floating duration which affected drug release profile**.** Formula 9 which contain 300 µl of AM (40% w/v), 20 mg PVA, 200 µl of Tween 20 (v/v), 3 mg (w/w) of TRFP, 45 µl of APS (20% w/v), 45 µl of TEMED (20% v/v), 130 mg of sodium bicarbonate was chosen as the optimum formula because of the proper physical properties. SPHC can be successfully utilized as drug delivery system for extending the release of drugs with low absorption therapeutic window.

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