THE USE OF KETOPROFEN NIOSOMES FOR FORMULATION OF SUSTAINED RELEASE TABLET DOSAGE FORM

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ABSTRACT

The objective of this study was to formulate sustained release tablet dosage form (100 mg) using Ketoprofen Niosomes. Ketoprofen Niosomes were prepared by lipid hydration method and then dried and compressed into sustained release tablets (100 mg). The tablet excipients employed include: Avicel PH 101, Avicel PH 102, and Mannitol as diluents, Cab-O-Sil (colloidal silica) as a glidant, Starch as a disintegrant and Magnesium Stearate as lubricating agent. The tablets were tested for weight variation, hardness, friability, thickness, disintegration, drug content and release ratio. Finally the release kinetics of Ketoprofen tablets were calculated.

Key words: Ketoprofen; Niosomes; lipid hydration method; sustained release tablets, direct compression

1. INTRODUCTION

Development of oral sustained release drug delivery systems is of much interest to the pharmaceutical scientists as these systems provide prolonged duration of action of drugs having short biological half-life, and reduce dose-related toxicity, dosing frequency, and patient non-compliance **(Chien, 1997; Uhrich *et al.*, 1999)**. Among the various sustained release drug delivery systems, pharmaceutical industries prefer sustained release tablet dosage form because of the ease of production using the existing tablet manufacturing infrastructure **(Bayomi *et al.*, 2001; Giunchedi *et al.*, 2000; Liew *et al.*, 2006)**. Various drug delivery techniques have been developed to sustain the release of drugs; recently colloidal particulate carriers such as Niosomes have been employed in drug delivery systems **(Shahiwala and Misra, 2002)**. Due to their capability to carry a variety of drugs, Niosomes has been extensively used in various drug delivery systems like controlled release **(Gupta *et al.*, 2005; Puglia *et al.*, 2004)**. Sustained release action of Niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via Niosomal encapsulation **(Jain *et al.*, 2006).** Ketoprofen has some disadvantages as the short half-life, low bioavailability and disturbance in the GI tract, so formulation of controlled release dosage forms is needed **(Palmieri *et al.*, 2002)**.

2. MATERIALS AND METHODS

2.1 Materials

Ketoprofen was kindly provided by El-Amyria Drug Company, Cairo, (Egypt), Span 60 from Sigma Chemical Co., Steinheim (Germany), Tween surfactants (20, 40, 60, and 80) from El-Nasr pharmaceutical Chemical Co., Cairo, (Egypt), Cholesterol from Sigma Chemical Co., St. Louis, MO, (USA), Sodium hydroxide and Potassium dihydrogen phosphate form El-Nasr Pharmaceutical Chemical Co., Cairo, (Egypt), Chloroform from Labscan Ltd, Dublin, (Ireland), Microcrystalline cellulose (Avicel® pH 101 and Avicel® pH 102) from Morgan chemical Ind. Co., Cairo, (Egypt), Amorphous fumed silica (Cab-O-Sil® M-5P), Cabot Corporation, North America, (USA), Magnesium Stearate, Prolabo (France),

Starch BP 68 from EL Nasr Pharm. Chem. Co., Cairo (Egypt), Mannitol from Sigma Chemical Co., St. Louis, MO, (USA)

2.2. Equipment

An electric balance (Mettler AJ100, Switzerland), Ultraviolet spectrophotometer (Jenway 6305 uv/vis, UK), Buchi rotavapor (R-3000, Switzerland), Magnetic stirrer (Type MMS, Germany), Probe Sonicator (Model 275T, Crest Ultrasonic Corp, New York, USA), Dissolution apparatus (Erweka TD6R, Germany), Shaker water bath (Julabo SW-20 C, Germany), Centrifuge (Biofuge, primo Heraeus, Germany), JEOL Transmission Electron Microscope (JTEM model 1010, Japan), Single Punch tablet press, (Royal Artist, Andheri (E), Bombay-400093, India), Tablet Hardness tester (Pharma test, Type PTB 301, Hainburg, Germany), Friability tester, (Pharma test, Type PTF1, Hainburg, Germany), Micrometer (M&W. Ltd, Sheffild, England), and Disintegration tester (Pharma test, Type PTZ3, Hainburg, Germany).

2.3. Methods

2.3.1. Preparation of Ketoprofen Niosomes

Ketoprofen Niosomes was prepared by lipid hydration method. The lipid mixture (30 %) of mixed surfactants (1:1 ratio of Span 60 with Tween 80) and cholesterol (1.5:1 ratio of mixed surfactants to cholesterol) were dissolved in 15 ml of chloroform. The solvent was evaporated using a rotary flash evaporator at speed (120 rpm), under low pressure at 60°C, which is above the gel–liquid transition temperature (T°c) of Span surfactants **(Abbas *et al.*, 2007; Azeem *et al.*, 2008)**. Niosomes were formed by adding phosphate buffered solution, PBS (pH 7.4) containing 2.5 % concentration of Ketoprofen slowly to the dried thin film formed on the walls of the round-bottom flask, with gentle agitation. The resulting Niosomal suspension was sonicated **(Ning *et al.*, 2005; Tejas *et al.*, 2002; Hao *et al.*, 2002)** using a probe sonicator, 20-kHz, and 500-W vibra cell at 1-min intervals for a period of 15 min.

2.3.2. Ketoprofen entrapment efficiency

The non-encapsulated Ketoprofen was separated from the Niosomal dispersions by centrifugation of the dispersion at 15,000 rpm for 45 min **(*Jaleh et al., 2003*)**. The supernatant was separated, diluted to 100 ml with PBS pH 7.4, filtered using a membrane filter (0.2 µm pore size), and measured using a spectrophotometer at 262 nm **(*Ibrahim et al., 2005*)**. The entrapment efficiency of Ketoprofen (EE (%)) was calculated by the following equation: EE %=[(C_t-C_r\C_t)] ×100% where C_t is the concentration of total Ketoprofen and C_r is the concentration of free Ketoprofen.

2.3.3. In-vitro release of Ketoprofen

This study was carried out using a USP dissolution tester (Apparatus I). After separation of the un-entrapped and adsorbed drug, the Ketoprofen Niosomal suspension (5ml) was placed in cylindrical tubes (2.5 cm in diameter and 6 cm in length). Each tube is tightly covered with a Spectra por© molecular porous membrane tubing from one end and attached to the shafts of the USP Dissolution tester apparatus, instead of the baskets, from the other end **(El-Laithy *et al.*, 2011)**. The shafts were then lowered to the vessels of the dissolution apparatus containing 250 ml of phosphate buffer (pH 7.4) so that the dissolution medium outside and the vesicles preparation inside were adjusted at the same level. The release study was carried out at 37±0.5 ºC, and the stirring shafts were rotated at a speed of 50 rpm. Five milliliter samples were withdrawn periodically at predetermined time intervals of 1, 2, 3, 4, 6, 8, 10, and finally 12 h. Every withdrawal was followed by replacement with fresh medium to maintain a constant volume. The samples were analyzed spectrophotometrically at 262 nm and the results were the mean values of three runs each representing one batch. The obtained release data were subjected to kinetic treatment according to zero, first, Higuchi diffusion models **(Higuchi, 1963)**, Hixson-Crowell cup root law **(Hixson and Crowell, 1977)** and Baker-Lonsdale equation **(Baker and Lonsdale,**

1974). The correlation coefficient (*r*), the order of release pattern and *t*50% value was determined in each case.

2.3.4. Transmission electron microscopy (TEM)

A sample drop was diluted 10-fold using de-ionized water and a drop of this diluted dispersion was applied to a collodion-coated 300 mesh copper grid and left for 5 min to allow some of the Niosomes to adhere to collodion. The remaining dispersion was removed by adsorbing the drop with the corner of a piece of filter paper. A drop of 2% aqueous solution of uranyl acetate was applied for 1 min. The remaining solution was then removed and the sample was air dried and examined with a transmission electron microscope.

2.3.5. Preparation of Ketoprofen tablets

The resultant dried sediment of the prepare Ketoprofen Niosomes which is equivalent to 100 mg of Ketoprofen (about 175 mg) after separation of un-entrapped drug (by centrifugation at 15000 for 45 min) was mixed with 325 mg of excipients; Starch was used as disintegrant in two different concentrations (5 and 15 %), Avicel (PH 101), Avicel (PH 102), and Mannitol were used as diluents, Cab-O-Sil (0.5 %) as a glidant, and Magnesium Stearate (1%) as a lubricant. Each formula ingredient was sieved through a 20-mesh size sieve, directly compressed into tablets using the single punch tablet press with flat-faced single punch. The machine was set with hardness of about 5 Kg/cm2 using flat punch 12 mm in diameter and had an average weight of about 500 mg. Six formulae as illustrated in table (1) were obtained.

Table (1): Composition of the suggested Ketoprofen formulations

Components (mg)	F1	F2	F3	F4	F5	F6
Dried Niosomes (Equivalent to 100 mg Ketoprofen)	175	175	175	175	175	175
Mannitol	-	-	-	-	292.5	242.5
Avicel PH 101	292.5	242.5	-	-	-	-
Avicel PH 102	-	-	292.5	242.5	-	-
Cab-o-sil	2.5	2.5	2.5	2.5	2.5	2.5
Starch	25	75	25	75	25	75
Magnesium Stearate	5	5	5	5	5	5

2.3.6. Physicochemical characterization of Ketoprofen tablets

Characterization of tablets was carried out according to the following parameters: mean weight, thickness, hardness, friability, drug content, disintegration time and dissolution test. Mean weight was determined according to the **British pharmacopoeia (B.P.), (2007)** (number of tablet (n) = 20). Thickness was determined according to the **B.P. (2007)** using micrometer (n = 20). Hardness and friability were carried out according to **B.P. (2007*)*** using a Pharma test hardness tester and Roche type friability (n =20). Disintegration was carried out according to the **B.P. (2007)** using Pharma test disintegration tester (n =10). Drug content was determined according to the **B.P. (2007)** (n = 10).

For the dissolution test, seven tablets from each formulation were used. The dissolution test was performed using the USP II basket method. Seven individual tablets from each formula were tested, each tablet was placed in basket, and the basket was rotated at 100 rpm in 250 ml of phosphate buffer pH 7.4 **(Jan *et al.*, 2011)**, and the temperature of the dissolution medium was maintained at 37°C ± 0.5 °C. Samples of 5 ml were withdrawn at regular time intervals 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours and replaced with an equal

volume of dissolution medium, filtered, and analyzed spectrophotometrically at 262 nm. The in-vitro release experiments were repeated in triplicate. Release kinetics of drug from all the tablets was also calculated.

3. RESULTS AND DISCUSSION

3.1. Characterization of the prepared formula of Ketoprofen Niosomes

The entrapment efficiency of the prepared formula was found to be equal 47.20±0.42%. The cumulative percent release of Ketoprofen from the prepared formula after one hour was 28.89%, after six hours was 71.64% and after twelve hours was 87.37%. The Kinetic models of the prepared formula were found to obey Higushi's diffusion model.

Transmission electron micrographs revealed the formation of well identified Niosomal vesicles as shown in figure (1). The examined Niosomes appeared as spherical unilamellar nano vesicles with sharp boundaries. Particle size analysis of the optimized formula shows that the size range lied between 162.32 and 288.14 nm (mean ٢١١.٢٢nm)

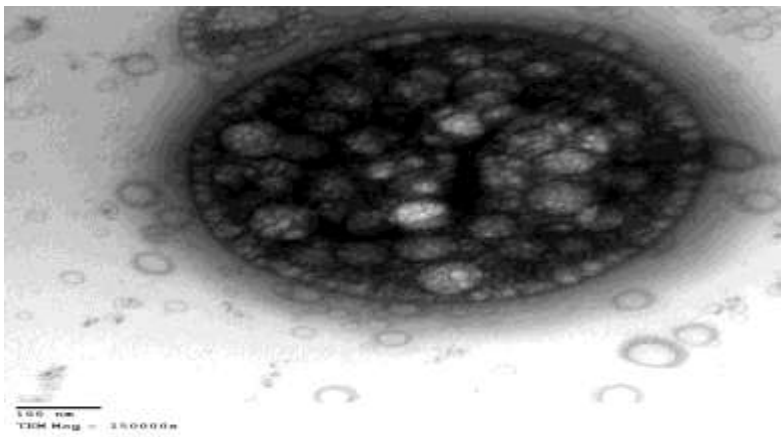

Fig.1. Transmission electron micrograph of the prepared formula

3.2. Physicochemical characterization of Ketoprofen tablets

As summarized in table (2); all the investigated Ketoprofen tablets showing that all formulations are within **B.P (2007)** limits.

Table (2): Physicochemical characterization of Ketoprofen tablets

Physicochemical characterization	F1	F2	F3	F4	F5	F6
Weight (gm)	0.4994±1.54	0.4998±1.01	0.4976±	0.4986±1.62	0.494±0.73	0.493±2.13
Thickness (mm)	3.444±0.05	3.622±0.10	3.532±0.13	3.526±0.09	3.660±0.13	3.872±0.07
Hardness (Kg)	8.13±0.82	8.47±0.39	8.854±0.99	8.912±0.71	6.43±0.35	6.72±0.37
Friability (%)	0.0148±0.32	0.0133±0.74	0.009±0.51	0.008±0.55	0.019±0.78	0.01914±0.95
Disintegration time (min)	7.4±1.78	8.4±1.48	9.6±1.54	10±1.58	12.2±1.92	13.4±1.76
Drug content (%)	98.856±2.96	98.098±2.08	96.372±1.17	97.012±1.13	95.738±2.07	95.63±1.55
Release (12hr)	86.94±1.20	91.81±0.99	73.8±0.84	76.92±0.87	80.45±1.11	84.37±1.02

3.2.1. Physical characterization of Ketoprofen tablets

From table (2), it was obvious that formulations containing Avicel PH 102 (formulations 3 and 4) presented higher hardness compared to those prepared with Avicel PH 101 (formulations 1 and 2). This agreed with **Bastos and Rossana (2008)** who have reported that blends prepared with Avicel PH 101 demonstrated a lower percentage of compressibility (16-18%) compared to blends containing Avicel PH 102 (18-21%). This may be explained also by some authors due to the higher surface area of Avicel PH 102 particles **(Pasqualoto *et al.*, 2005; Doelker *et al.*, 1995; Hdenp *et al.*, 1997)**. This agreed with **Rowe *et al.* (2005)** who have reported that particles of Avicel PH 102 have a larger surface area (1.21-1.30 m2.g-1)) compared to the particles of Avicel PH 101 (1.06-1.12 m2.g-1). These previous reports can justify the higher hardness of tablets prepared with Avicel PH 102 than those prepared with Avicel PH 101. On the other hand, regarding the evaluation of the friability of tablets, the present study showed that formulations prepared with Avicel PH102 presented a lower friability, which agrees to the result from hardness previously discussed.

Moreover, formulations containing Avicel (PH 101 and 102) (F1-F4) presented higher hardness compared to those prepared with Mannitol (F5 and F6). Higher hardness corresponding to the interaction between microcrystalline cellulose and colloidal silicon dioxide; microcrystalline cellulose particles are preferentially coated by colloidal silicon dioxide and by showing the great interaction forces between microcrystalline cellulose and colloidal silicon dioxide particles, resulting in increasing the hardness **(Bastos and Rossana, 2008)**.

Formulations containing Avicel (PH 101 and 102) (F1-F4) presented shorter disintegration time compared to those prepared with Mannitol (F5 and F6). Beside the higher hardness and lower friability of Avicel containing formulations, it has disintegration properties producing synergistic effect with starch and hence it has a good effect on the disintegration time. On the other hand, Mannitol has good aqueous solubility, negative heats of solution and good wetting properties, these attributes improve the binding of the tablets and water uptake, thereby decreasing disintegration time **(Jashanjit and Rajmeet, 2009)**.

Furthermore, formulations containing low concentration of Starch (formulations 1, 3, and 5) presented lower hardness, lower friability, and shorter disintegration time compared to those prepared with high concentration of Starch (formulations 2, 4, and 6). This agreed with **Narmada *et al.* (2009)** who reported that as the concentration of starch increases, hardness also increases. This was explained by **Oyi *et al.* (2009)** who reported that as the more starch is forced into interparticulate spaces thereby increasing the area of contact between the particles leading to formation of additional solid bonds and these confer resistance to tablet fracture and abrasion (increase hardness), thereby bringing about a decrease in friability. This also led to a corresponding reduction in the size of the capillary spaces between the particles (leading to the decrease in the friability). This reduction in capillary spaces led to the reduction in the penetration of water into the tablet to cause bond separation and thus, leading to longer disintegration times.

However, the effect of the type of diluent and concentration of disintegrant were clearly observed in the results of hardness, friability, and disintegration time.

3.2.2. In vitro release study of Ketoprofen from Ketoprofen tablets

Figure (2) showed the release profiles of Ketoprofen from Ketoprofen tablets. The release profiles of Ketoprofen from tablets were occurred in two distinct phases (biphasic release processes), an initial phase in which rapid drug leakage was observed and stayed for about 8 hours, followed by slow phase stayed at least for 4 hours. This is an indication that the release of Ketoprofen from the prepared tablets is controlled release.

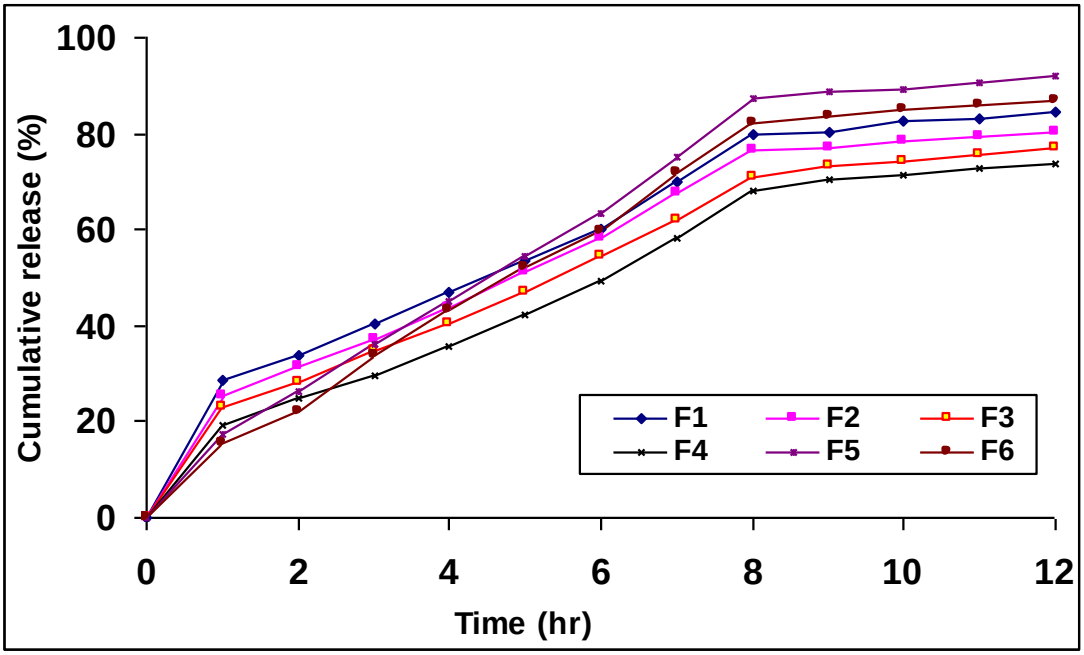

Fig.2. Ketoprofen release profiles from Ketorpofen tablets (F1-F6)

From the in vitro release profiles, we can indicate that, the slow release of Ketoprofen from the prepared tablets ensures that the drug is available for a longer period of time and that too without degradation. The release data indicate that Ketoprofen tables were effective in their release characteristics, as controlled release tablets.

Also from Ketoprofen release profiles, it was obvious that formulations containing Avicel PH 101 (formulations 3 and 4) presented higher release % compared to those prepared with Avicel PH 102 (formulations 1 and 2). This can be explained by higher hardness corresponding to a higher interaction among the large particles of Avicel PH 102 which could lead to the slow release of Ketoprofen. On the other hand, this result could be related to the lower hardness of tablets prepared with Avicel PH 101. This agreed with **Alderborn (2005)** who reported that formulations containing Avicel PH 101 presented the highest mean drug release.

Moreover, formulations containing Mannitol (F5 and F6) presented higher release % compared to those prepared with Avicel (PH 101 and 102) (F1-F4). This can be explained by the higher hardness of Avicel preparations, as the hardness of the tablets is increased the capillary pores are reduced and the penetration of dissolution medium into the tablets is decreased and ultimately there is less dissolution of drugs. This was agreed with **Frederic (2010)** who reported that the dissolution rate of the drug was decreased as the Avicel was increased. Another explanation may be due to the lower wettability of Avicel. This was agreed with **Elsayed *et al* (2011)** who reported that Avicel is insoluble in water; therefore, it may decrease the wettability of Paracetamol and thus decrease its release. On the other hand Mannitol is highly soluble filler so provide the fast rate of drug release (**Gaston *et al.*, 2008)**.

Furthermore, formulations containing low concentration of Starch (formulations 1, 3, and 5) presented higher release % compared to those prepared with high concentration of Starch (formulations 2, 4, and 6). The decrease in the release % upon increase in the concentration of starch was explained by **Odeku *et al.* (2006)** who have reported that this decrease could be due to its high bond strength and lower swelling capacity which could be responsible for the increase in dissolution time.

However, the effect of the type of diluent and concentration of disintegrant were clearly observed in the in vitro release results of Ketoprofen.

Table (3) shows the release kinetics of Ketoprofen tablets. The best kinetic order for the in-vitro release of Ketoprofen was calculated from the highest values of the obtained correlation coefficients. The kinetic analysis of all release profiles followed diffusion controlled mechanism with an initial relative fast release phase followed by a slower release one. Similar results were obtained by **Kuksal *et al.* (2006)** who have reported that drug release data of conventional tablet was fitted in first order equation (r2 = 0.9256), while drug release data of batch A and B matrix tablets showed good fit into the Higuchi equation (r2 = 0.9837 and 0.9856, respectively).

Table (3): Kinetic analysis of the release data of Ketoprofen from different prepared tablets

F. No	Model	R	K	$t_{1/2}$	Order
F1	Zero-order	٠.٩٧٤	٥.٦٢٩	٨.٨٨٢	Diffusion model
	First-order	٠.٩٨١	٠.١٥٨	٤.٣٦١	
	Second-order	٠.٩٦٩	٠.٠٠٥	١.٩٢٢	
	Higuchi's diffusion model	٠.٩٨٣	٢٦.٢٣٠	٣.٦٣٣	
	H-C	٠.٩٨١	٠.١٧١	٥.٥٨٨	
	B-L	٠.٩٧٦	٠.٠٢١	٢.٥٠٤	
F2	Zero-order	٠.٩٧٠	٥.٥١٧	٩.٠٦٢	Diffusion model
	First-order	٠.٩٧٩	٠.١٣٩	٤.٥٩٨	
	Second-order	٠.٩٧٣	٠.٠٠٣	٢.٥١٨	
	Higuchi's diffusion model	٠.٩٨٢	٢٥.٧٩٣	٣.٧٥٧	
	H-C	٠.٩٧٨	٠.١٥٦	٦.١٠٧	
	B-L	٠.٩٧٥	٠.٠١٩	٢.٨٨٣	
F3	Zero-order	0.977	5.383	9.287	Diffusion model
	First-order	0.985	0.123	5.593	
	Second-order	0.979	0.003	3.199	
	Higuchi's diffusion model	0.986	25.074	3.976	
	H-C	0.984	0.143	6.654	
	B-L	0.981	0.016	3.313	
F4	Zero-order	0.976	5.549	9.009	Diffusion model
	First-order	0.980	0.118	5.866	
	Second-order	0.973	0.002	3.664	
	Higuchi's diffusion model	0.981	25.747	3.770	
	H-C	0.980	0.140	6.792	
	B-L	0.973	0.015	3.609	
F5	Zero-order	0.967	7.322	6.872	Diffusion model
	First-order	0.977	0.239	2.895	
	Second-order	0.951	0.010	0.919	
	Higuchi's diffusion model	0.983	34.391	2.113	
	H-C	0.979	0.240	3.974	
	B-L	0.969	0.031	1.739	
F6	Zero-order	0.966	7.053	7.089	Diffusion model
	First-order	0.980	0.194	3.561	
	Second-order	0.965	0.006	1.491	
	Higuchi's diffusion model	0.984	33.170	2.272	
	H-C	0.980	0.209	4.566	
	B-L	0.973	0.025	2.116	

4. CONCLUSION

The overall results of this study showed that Ketoprofen tables were effective in their release characteristics, as sustained release tablets. However, the effect of the type of diluent and concentration of disintegrant were clearly observed. Avicel PH 101 and 5 % concentration of starch (lower concentration) gave the best effect on the Ketoprofen tablets.

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صياغة عقار الكيتوبروفين المحمل علي النيوزومات في صيغة الأقراص ذات الإنطلاق الدوائي المستمر والمنتظم

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تهدف هذه الدراسة الي صياغة عقار الكيتوبروفين المحمل علي النيوزومات في صيغة الأقراص ذات الإنطلاق الدوائي المستمر والمنتظم. قد تم تحضير الكيتوبروفين المحمل علي النيوزومات بطريقة تميؤ المادة الدهنية ثم تم تجفيفه وكبسه بطريقة الكبس المباشر في صورة أقراص ذات إنطلاق مستمر ومنتظم (١٠٠ مجم). صواغات الأقراص المستخدمة تشمل آفيسيل بي اتش ١٠١، افيسيل بي اتش ١٠٢، و المانيتول كحوامل للعقار، كابوسيل كمادة تساعد في الانسيابية، نشا كمادة تساعد في التفتت إضافة إلى شمعات الماغنسيوم كمادة زالقه. كما أجريت اختبارات الجودة للأقراص المحضرة وهي دراسة اختلاف الوزن، اختلاف السمك، الصلابة، الهشاشة، زمن التفتت، المحتوى الدوائي للأقراص، معدل الإنطلاق المعملي. وأخيرا تم تعيين حركية الإنطلاق للعقار.