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PREPARATION AND EVALUATION OF SUSTAINED-RELEASE DICLOFENAC SODIUM TABLETS

Hussein Abdulmoneim Sayed, Mamdouh Moustafa Ghorab and Tamer Hassanen Hamed
Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt

ABSTRACT

The aim of this work is to prepare and evaluate sustained-release matrix diclofenac sodium (DS) tablets using simple diluents by either direct compression or wet granulation techniques. The prepared tablets were evaluated for physical characteristics and in vitro dissolution rate, and the results were compared to a standard commercial product (Voltaren® 100 SR tablets). The effect of cetyl alcohol (CA) amount on the physical characteristics of DS tablets prepared by wet granulation using a mixture of dibasic calcium phosphate:Avicel PH102 as a diluent was studied. The results show that tablets prepared with a mixture of dibasic calcium phosphate:Avicel PH102 as a diluent using wet granulation technique are superior in the release rate retardation. Increasing CA amount results in an increase in tablet disintegration time, a decrease in tablet friability, and retardation in DS release. As a conclusion, formulations prepared by wet granulation show a lower release rate in both acidic and buffer media compared to those prepared by direct compression using the same diluent, and increasing CA amount above 30 mg does not significantly affect the release rate but has a significant effect on release mechanism and release kinetics.

INTRODUCTION

Controlled release (CR) drug delivery systems are used to improve the therapeutic response by providing blood levels that are more consistent and stable compared with immediate release dosage forms[1]. FDA defines an extended release (ER) dosage form as one that allows a reduction in dosing frequency as compared to that presented by a conventional dosage form[2].Matrix tablets are one of the most attractive and widely used oral CR systems[3-5]. It consists of drug dispersed homogenously throughout a polymer matrix[4,6]. Suitable combination between various types of polymers, as matrix-forming materials, enables appropriate modification of the release characteristics of drugs from CR dosage forms[5-12].

Diclofenac sodium (DS), sodium [o-(2,6-dichloroanilino)phenyl]acetate, is a potent non-steroidal anti-inflammatory drug (NSAID) with pronounced analgesic and antipyretic properties[12-14]. Comparative studies have shown that DS is at least equivalent in efficacy to aspirin and other NSAIDs when used for the treatment of rheumatic diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and migraine[13-19].

In view of the physicochemical, pharmacokinetic and pharmacodynamic characteristics of DS, the drug is found to be very interesting in ER oral dosage forms, especially for its relative short biological half-life, the hazards of adverse GIT reactions, and chronic nature of treatment[20,21]. In addition, the method by which modified release is achieved can improve the bioavailability of DS and reduce the average cost of treatment over an extended period[13]. The release of DS from CR formulations was found to be strongly medium dependent[22,23]. Also, rotation speed of the stirring element, and ionic strengths of the dissolution medium have a significant impact on the release of DS[23].

The aim of this work is to prepare an ER DS tablets using simple diluents with or without cetyl alcohol as a release retardant. The release kinetics of the prepared tablets will be in vitro evaluated. The results will be compared to a commercial product (Voltaren® 100 SR) tablets.

MATERIALS AND METHODS

Materials:

- Diclofenac Sodium BP 93 (Arzneimittelwerk Dresden GmbH Company, Trittau, Germany).
- Voltaren® 100 SR Tablets (Novartis Pharmaceutical Company, Cairo, Egypt).
- Dibasic Calcium Phosphate Anhydrous USP 22 (El-Nasr Pharmaceutical Chemicals Company, Cairo, Egypt).
- Avicel PH-102 (FMC Corp., Philadelphia, PA, USA).
- Magnesium Stearate, (Merck, Darmestadt, Germany).
- Hydroxypropylmethylcellulose, Methocel E5 (Dow Chemicals, USA).
- Cetyl Alcohol (El-Nasr Pharmaceutical Chemicals Company, Cairo, Egypt).
- Aerosil 200, (CABOT Corp. Tuscola, IL, USA).
- All other chemicals were of analytical grades and were used as received.

Equipments:

- Shimadzu Double Beam UV-Visible Spectrophotometer, model UV- 1601PC (Shimadzu Corporation, Kyoto, Japan).
- Dissolution Tester, Six Cups, model TDD-6 (S.B.S. Instruments, Barcelona, Spain).
- Multi-Purpose Thickness Tester, model HC-10 (Shanghai, China).
- Disintegration Tester, model TDI-1 (S.B.S. Instruments, Barcelona, Spain).
- Abrasion Tester (Friabilator), model TDA-1 (S.B.S. Instruments, Barcelona, Spain).
- Digital Tablet Hardness Tester, model C-DHT100 (Campbell Electronics, Maharashtra, India).
- Sieves and Mechanical Shaker, type As200basic, F.Kurt (Retsch GmbH Company, Germany).
- Pilot Press Tablet Machine, model CPMD 3 – 10. 10 Station Pilot Press GMP Model, (Chamunda Pharma Machinary Pvt. Ltd, Ahmedabad, India).

Methods:

Construction of calibration curve of diclofenac sodium:

An accurately weighed amount of DS was dissolved in methanol to obtain a stock solution with a content of 1000 µg/ml. Aliquot (1ml) was transferred to 50 ml volumetric flask, the volume was completed with distilled water, 0.1N hydrochloric acid, or phosphate buffer of pH 7.2 and mixed well to obtain a solution with a content of 20 µg/ml. Series of solutions containing different contents of DS (0.5 – 30 µg/ml) were prepared and the absorbance of each was measured at the maximum absorbance of DS (276nm) using either distilled water, 0.1 N hydrochloric acid or phosphate pH 7.2 as a blank.

Diclofenac sodium tablet formulation:

The different tablet formulations were prepared by direct compression or wet granulation techniques as follows:

Direct compression: DS and diluents were individually sieved (sieve number 50, 300 µm) before being geometrically mixed by spatulation on a clean paper sheet for 15 minutes. Magnesium stearate was sieved on the powder mixture and mixed for 5 minutes. Tablets were compressed using rotary tabletting machine (8 mm die, and biconcave punches) that was adjusted to produce tablets weighing 300 mg. Table (1) summarizes composition of F1 and F2 formulations prepared by direct compression.

Wet granulation: DS and diluents were individually sieved (sieve number 50, 300 µm) before being geometrically mixed. Powders were granulated using HPMC (Methocel E5) solution followed by cetyl alcohol alcoholic solution until dough mass was obtained then passed through sieve number 35 (500 µm). The formed granules were dried at 50°C for 6 hours in the oven. Dried granules were then sieved and the fraction passed from 500 µm sieve and retained on 300 µm sieve was collected. Magnesium stearate and Aerosil were sieved on the granules and mixed for 5 minutes. Tablets were compressed using rotary tabletting machine (8 mm die, and biconcave punches) that was adjusted to produce tablets weighing 300 mg. Table (1) also summarizes composition of F3 to F7 Formulations prepared by wet granulation.

Physical characterization of the prepared tablets:

The physical parameters (weight uniformity, thickness, hardness, friability, and disintegration time) as well as content uniformity of all the formulations were determined according to the USPXXX methods.

Dissolution testing:

The dissolution testing was performed according to the USPXXX specifications using apparatus I (basket) at 100 rpm. Tested dissolution media (900 ml) were either 0.1N hydrochloric acid (pH 1.2), or phosphate buffer (pH 7.2). At different time intervals, 5ml samples were withdrawn using millipore filter head (0.45 µm) and an equal volume of fresh preheated dissolution medium was replaced. DS content was determined spectrophotometrically at 276 nm against a blank solution containing the same buffer system, (n=3). Because of the instability of DS in acidic medium, a correction factor for samples tested at pH 1.2 was added. The data obtained was kinetically analyzed using zero order, and first order kinetics as well as Higuchi diffusion model[7].

Table (1): Diclofenac sodium formulations prepared by either direct compression or wet granulations.

	F. Code	CP	A	H	CA	Aer	M
1	F1	197	----	----	----	----	3
2	F2	98.5	98.5	----	----	----	3
3	F3	180.4	----	6	10	0.6	3
4	F4	90.2	90.2	6	10	0.6	3
5	F5	85.2	85.2	6	20	0.6	3
6	F6	80.2	80.2	6	30	0.6	3
7	F7	75.2	75.2	6	40	0.6	3

Where **CP**; Dibasic Calcium Phosphate, **A**; Avicel PH102, **H**; HPMC (Methocel E5), **CA**; Cetyl Alcohol, **Aer**; Aerosil, and **M**; Magnesium Stearate

RESULTS AND DISCUSSION

Construction of calibration curve of Diclofenac sodium:

Fig (1) shows linear relationship with a regression values (r^2) of 0.9991, 0.9983, and 0.9997 in distilled water, 0.1N hydrochloric acid or buffer at pH 7.2 respectively, at contents range of 0.5 - 30 µg/ml.

Physical characterization of the prepared tablets:

The physical parameters of all formulations prepared by direct compression and wet granulations as well as drug content are shown in Table (2). All parameters were within pharmacopeial specifications. There is no significant difference in physical characteristics of DS tablets prepared by direct compression (F1, and F2) and those prepared by wet granulation technique (F3, and F4) except that tablets prepared by wet granulations showed a higher disintegration time and lower friability.

Dissolution testing:

Dissolution profile of formulations prepared either by direct compression or wet granulation at pH 1.2, and pH 7.2 are shown in Fig (2), and (3) respectively.

For dibasic calcium phosphate Formulations, F3 formulation prepared by wet granulation showed a lower release rate in both acidic and buffer media to that prepared by direct compression (F1).

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Table (2): Physical characteristics of different formulations containing diclofenac sodium prepared by either direct compression or wet granulation (mean ± SD)

F. Code	Thickness (mm) n = 20	Weight (mg) n =20	Drug content (%) n = 6	Hardness (kg) n = 10	Friability (%) n = 20	Disintegration time (min) n = 6
F1	03.96 ± 0.02	304.44 ± 1.76	101.74 ± 0.01	17.48 ± 1.01	0.41	25.36 ± 1.56
F2	04.40 ± 0.03	299.95 ± 1.96	104.51 ± 0.01	25.33 ± 0.63	0.07	20.77 ± 0.23
F3	04.00 ± 0.01	302.17 ± 1.53	102.56 ± 0.02	16.63 ± 0.46	0.19	37.92 ± 1.50
F4	04.48 ± 0.01	299.00 ± 0.89	100.62 ± 0.01	30.45 ± 0.66	0.17	92.50 ± 2.50
F5	04.56 ± 0.02	300.87 ± 1.68	97.98 ± 0.03	29.47 ± 0.66	0.05	113.50 ± 4.00
F6	04.69 ± 0.01	300.90 ± 1.97	97.36 ± 0.02	29.30 ± 0.68	0.01	133.75 ± 0.25
F7	04.81 ± 0.02	301.14 ± 1.21	98.44 ± 0.02	29.28 ± 0.28	0.00	169.29 ± 0.94

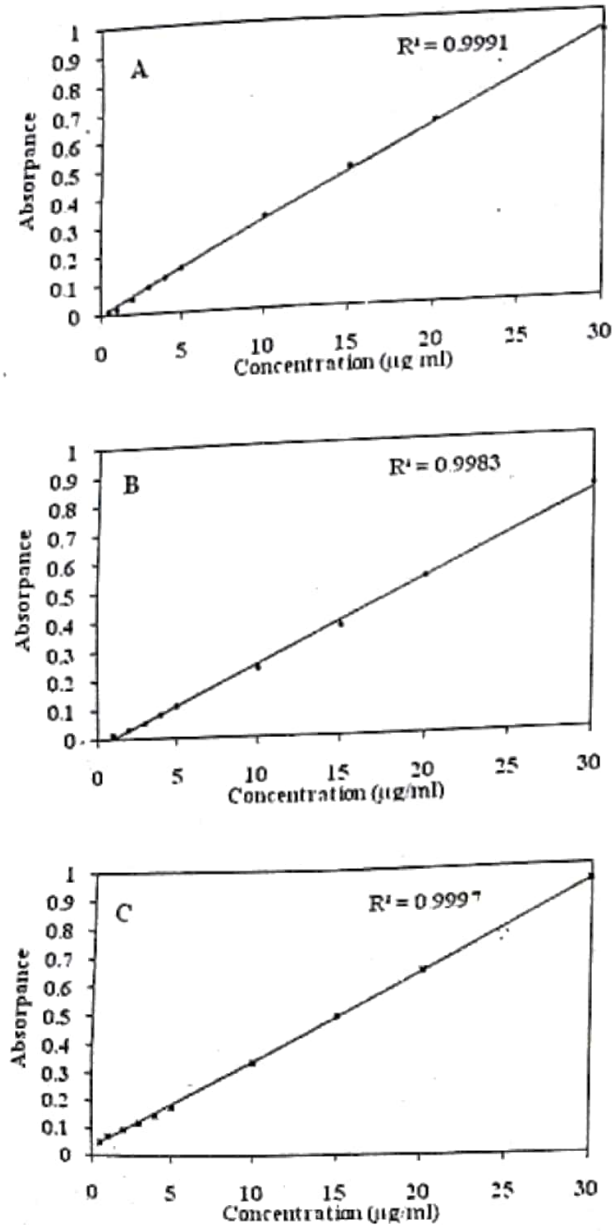

Fig (1): Standard calibration curves of diclofenac sodium in different solvent media (A; Distilled Water, B; pH 1.2, and C; pH 7.2).

The same was observed when mixture of Avicel:dibasic calcium phosphate was used as a diluent; F4 formulation gave a lower release rate than F2 formulation. Also, formulations prepared using mixture of Avicel:dibasic calcium phosphate in the ratio of 1:1 w/w as diluents (F2, and F4) were superior in DS release rate retardation than formulations prepared using dibasic calcium phosphate as a diluent (F1, and F3).

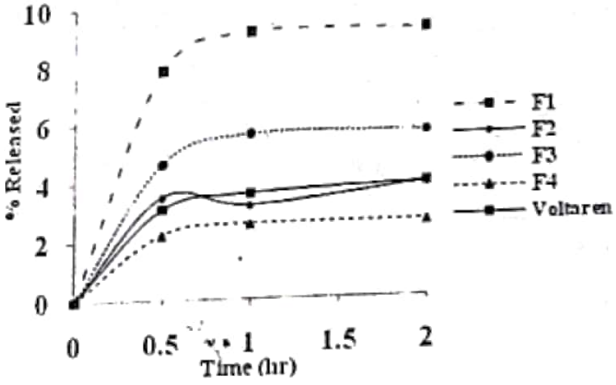

Fig (2): Dissolution profile of formulations prepared either by direct compression or wet granulation at pH 1.2

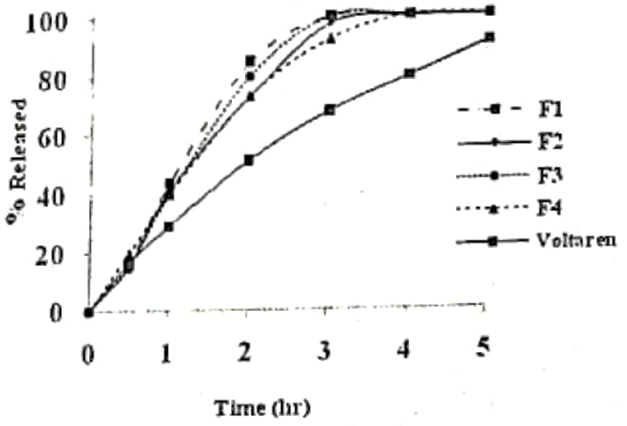

Fig (3): Dissolution profile of formulations prepared either by direct compression or wet granulation at pH 7.2.

This is may be due to the addition of Avicel that resulted in hardness increase that accounted for the observed release retardation. However, in buffer media, all formulations showed higher degree of abrasion and failed to give a release rate closer to that of Voltaren® 100 SR tablets.

Effect of cetyl alcohol amount on the characteristics of diclofenac sodium tablets prepared by wet granulation:

The effect of CA on the physical characters of DS tablets prepared by wet granulation (F4 – F7) using different contents of CA (10, 20, 30, and 40 mg) is shown in Table (2). It is cleared from the data that by increasing the amount of CA, a decrease in friability while an increase in tablet disintegration time occurs. The effect on hardness was non-significant.

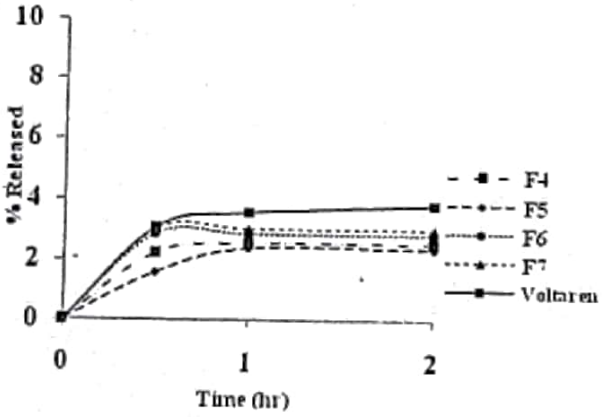

Fig (4): Dissolution profile of formulations prepared by wet granulation using different contents of cetyl alcohol at pH 1.2.

Fig (4) and Fig (5) show the dissolution profile at pH 1.2 and pH 7.2 respectively of formulations prepared by wet granulation using different contents of CA. Results revealed that increasing CA content successfully retarded DS release in acid medium. However, in buffer media, increasing CA content up to 20 mg/tablet (F5) did not retard DS release. Reaching CA content up to 30 mg/tablet (F6) significantly retarded DS release. Further increase in CA (F7) showed a non significant retardation in DS release. Matrix integrity was also significantly improved when CA amount was 30 mg or more (F6 and F7). Tablets prepared with CA content of 30 and 40 mg were slowly eroded all over the dissolution testing period without any matrix disintegration.

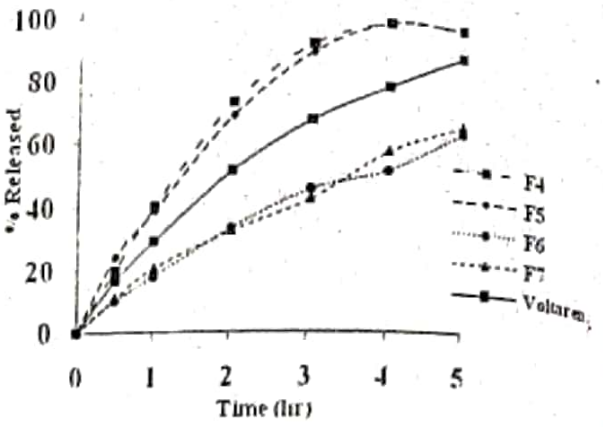

Fig (5): Dissolution profile of formulations prepared by wet granulation using different contents of cetyl alcohol in pH 7.2.

In vitro release kinetics from selected tablet formulations:

Based on dissolution data in phosphate buffer (pH 7.2), only F6, and F7 formulations had an acceptable DS release retardation comparable to Voltaren® 100 SR. Formula F7 was superior in retaining matrix integrity. It is cleared in Table (3) that DS released from F6 formula is best fitting Higuchi model kinetics and F7 formula is best fitting zero order kinetics.

CONCLUSION

Formulations prepared by wet granulation showed a lower release rate in both acidic and buffer media than those prepared by direct compression suing the same diluent. Tablets containing a mixture of dibasic calcium phosphate:Avicel PH102 (1:1 w/w) as a diluent prepared by wet granulation is superior in both release rate retardation and matrix integrity.

In general, increasing CA content results in an increase in tablet disintegration time, and a decrease in tablet friability. Increasing CA amount above 30 mg does not significantly affect the release rate but has a significant effect on release mechanism and release kinetics. F7 formula was superior in retaining matrix integrity during the high abrasion forces developed during basket operation. However, DS release rate had to be modulated using different process variables to enhance DS release kinetics.

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Table (3): In vitro release kinetics data of diclofenac sodium from f6 and f7 formulations using basket at 100 rpm as a dissolution apparatus at pH 7.2.

	Zero order			First order			Higuchi model		
	Intercept	K_0	r^2	Intercept	K_1	r^2	Intercept	K_H	r^2
F6	6.53	11.92	0.986	21.49	23.20	0.954	- 16.39	35.46	0.992
F7	6.60	12.45	0.994	22.51	23.83	0.930	- 16.86	36.73	0.984

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تحضير و تقييم أقراص الديكلوفيناك صوديوم الممتدة المفعول

حسين عبد المنعم سيد، ممدوح مصطفى غراب، تامر حسنين حامد

قسم الصيدلانيات والصيدلة الصناعية – كلية الصيدلة – جامعة قناة السويس–الاسماعيليه–مصر

يهدف البحث الى تحضير و تقييم أقراص ديكلوفيناك صوديوم الممتدة المفعول بأستخدام بعض السواغات البسيطة عن طريق الكبس المباشر أو التحبيب المبلل. تم تقييم اللأقراص المحضرة عن طريق دراسة خواصها الفيزيقية و كذلك دراسة معدل انطلاق الديكلوفيناك صوديوم من الأقراص و مقارنتها بالأقراص القياسية المتداولة في السوق المصري (فولتارين ١٠٠ اس.ار.). تشير النتائج الى أن الأقراص المحتوية على مزيج من فوسفات الكالسيوم ثنائي القاعدية مع الأفسيل كسواغ و المحضرة بطريقة التحبيب المبلل كانت الأفضل في معدل الأنطلاق كذلك في المحافظة على سلامة شكل القرص. تم دراسة تأثير كمية كحول السيتيل على الخواص الفيزيقية و معدل انطلاق الديكلوفيناك صوديوم من الأقراص المحضرة بطريقة التحبيب المبلل بأستخدام سواغات مختلفة. و قد وجد أن زيادة كمية كحول السيتيل ينتج عنها زيادة في وقت تفتت القرص و نقص في نسبة هشاشته. كذلك زيادة كمية كحول السيتيل ينتج عنها نقص ذو مغزى في معدل انطلاق الديكلوفيناك صوديوم من الأقراص و له أيضاً تأثير ذو مغزى في ميكانيكية و حركية الأنطلاق من القرص و المحافظة علي سلامة القرص.