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PREPARATION AND EVALUATION OF DIRECTLY-COMPRESSED INDOMETHACIN, INDOMETHACIN SODIUM AND INDOMETHACIN MEGLUMINE TABLETS

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ABSTRACT

A formula containing Compactrol, Ac-Di-Sol,Aerosil 200 and talc was used to prepare directly-compressed tablets of indomethacin and its sodium and meglumine salts. The prepared tablets were evaluated for uniformity of weight and thickness, hardness, friability and content uniformity. Each batch was then divided into two, one was coated with an opaque non-enteric film coat and evaluated for coat thickness uniformity. The dissolution rates of the uncoated and coated tablets and the effect of shelf-storage, at room temperature for 11 months, on drug contents were also studied. Indomethacin meglumine tablets showed the least relative standard deviation of weight and thickness. They exhibited acceptable uniformity of content and coat thickness, and the highest hardness-friability ratio. Also exhibited, uncoated and coated, the best in-vitro release of its drug contents and the maximal stability.

INTRODUCTION

Indomethacin is one of the most widely used non-steriodal anti-inflammatory drug with antipyretic and analgesic properties. Several trials have been made to abolish or minimize its side effects. The scope of them is summarized in three main ways; coadministration of indomethacin and prostaglandins (1), preparation of a sustained release dosage form (2) and pro-drug formation (3-5).

In this work, two indomethacin derivatives were chosen, indomethacin sodium (6) and indomethacin meglumine (7,8), and comparative studies were done on them and the free acid form, indomethacin (9), after formulating them as directly compressed tablets. The tablets were prepared using a formula which was considered by DSC to be the formula of choice for the three drugs (10), and were evaluated for uniformity of weight and thickness, hardness, friability and content uniformity. Half of the prepared tablets were film-coated using opaque non-enteric coat, to guard against photosensitivity (11), and evaluated for coat thickness uniformity. The uncoated and coated tablets were then subjected to dissolution testing and shelf-storage at room temperature for 11 months.

EXPERIMENTAL

Materials

Indomethacin (donated by Misr Co.for Pharm. Ind., Cairo, Egypt), indomethacin meglumine (donated by The Nile Co.for Pharmaceutical and Chemical Industries, Cairo, Egypt), indomethacin sodium, Ac-Di-Sol, Aerosil 200, talc,hydroxypropyl methylcellulose, titanium dioxide and PEG 4000 (donated by EIPICO Co., 10th of Ramadan, Egypt), Compactrol (E. Mendell Co.,Inc.,Carmel,

N.Y., U.S.A.) were used. All other materials were of analytical reagent grade.

Tablet Preparation

The components of each formula (Table 1) were mixed together for 15 minutes in a drum mixer. Tablets were prepared on a single punch tabletting machine (Erweka, Type EK:0, Frankfurt, Germany) using flat 10 mm punches and with hardness of about 6 kg/cm^2. The tabletting machine was set to produce tablets with an average weight of 0.34 g for indomethacin and indomethacin sodium tablets, and 0.36 g for indomethacin meglumine tablets.

Film Coating

Half of the prepared tablets were rotated in a coating pan (Brucks, Type VII G, Leine, Germany) and sprayed by a spray-gun atomizer device with a coating solution containing: hydroxypropyl methylcellulose; 144 g, PEG 4000; 36 g, titanium dioxide; 200g, ethanol; 600 g and methylene chloride; 500 g, and dried by hot air stream. The coated tablets were then dried overnight in a drying oven at 35°C.

Tablet Evaluation

Twenty tablets were tested for uniformity of weight (12) and the thickness of each weighed tablet was measured using a micrometer (M&W LTD., Sheffield, England). The hardness of 10 tablets was measured using Pharma Test Tablet Hardness Tester (Type PTB 301, Germany). Friability was tested five-times,20 tablets each,in a Pharma Test Friabilator (Type PTF 1,Germany). The coat thickness of 100 tablets was measured using a micrometer and it equals the mean difference between the thickness of coated and uncoated tablets.

TABLE 1

Composition and Evaluation of Directly Compressed Indomethacin, Indomethacin Sodium and Indomethacin Meglumine Tablets.

Tablet Composition	Indomethacin	Indomethacin Sodium	Indomethacin Meglumine
Drug	7.0%	8.5%	10.5%
Compactrol	85.0%	80.5%	77.0%
Ac-Di-Sol	2.0%	2.0%	2.0%
Talc	4.5%	6.5%	6.0%
Aerosil 200	1.5%	2.5%	4.5%
Tablet Evaluation			
Weight uniformity (mg)			
Mean ± SD	343.2±0.869	341.3±1.673	362.4±0.548
Range	341.5-344.9	338.6-344.0	361.5-363.3
RSD_a	0.253	0.490	0.151
Thickness uniformity(mm)			
Mean ± SD	3.47 ± 0.09	3.46 ± 0.20	4.30 - 0.09
Range	3.35 - 3.65	3.30 - 3.85	4.20 - 4.40
RSD	2.59	5.78	2.09
Hardness (kg)			
Mean ± SD	2.20 ± 0.15	2.00 ± 0.19	6.60 ± 0.53
Range	1.30 - 3.10	1.10 - 4.10	3.70 - 8.20
RSD	6.80	9.50	8.03
Friability (%)			
Mean ± SD	0.528±0.010	0.617±0.020	0.214±0.009
Range	0.340-0.682	0.481-0.763	0.195-0.390
RSD	1.89	3.24	4.20
$H.F.R._b$	4.17	3.24	30.84
Content uniformity (%)			
Mean ± SD	98.78±1.18	98.90±1.50	101.82±1.46
Range	96.2-101.1	96.5-102.1	99.8-104.5
RSD	1.19	1.51	1.43
95% TSUCL of RSD_c	1.84	2.30	2.147
Coat thickness (mm)			
Mean ± SD	0.13±0.008	0.14±0.007	0.13±0.008
Range	0.035-0.285	0.117-0.287	0.105-0.255
RSD	6.15	5.00	6.15
Drug remained after 11 months (%)			
Uncoated tablets:			
Mean ± Sd	96.65±1.18	75.59±0.98	100.00±1.03
Range	95.64-98.31	74.48-76.87	99.12-101.45
RSD	1.22	1.30	1.03
Coated tablets:			
Mean ± SD	97.50±0.56	72.30±1.75	100.3±0.65
Range	96.91-98.26	76.16-74.44	99.5-101.1
RSD	0.57	2.42	0.65

[a] RSD = Relative standard deviation (100 s/$\bar{x}$)

[b] H.F.R.= Hardness friability ratio

[c] 95% TSUCL of RSD = 95% two-sided upper confidence limit of relative standard deviation

Analytical Procedures

For the content uniformity of dosage units (13),10 tablets from each batch were powdered separately and transferred to a 100 ml volumetric flask and diluted with methanol to volume. After mixing and filtration (0.45 μm), 10 μl of this solution was used as sample for the HPLC analysis (Beckman System Gold, Programable Solvent Module 116,Programable Detector 166, U.S.A.). The mobile phase consisted of methanol; 55, acetonitril; 10, water; 35 and acetic acid; 1. The column was Ultrasphere ODS C_{18}, 7 cm x 4.6 mm I.D. (Beckman, U.S.A.). The detector was ultraviolet λ 254 nm, System Gold (Beckman, U.S.A.). The amounts of indomethacin equivalents were determined by comparing the peak area with a standard solution of indomethacin in methanol.

For dissolution testing, Pharma Test Dissolution Apparatus (Type PTW, Germany), was used. The paddel was rotated at 100 rpm and the dissolution medium was 900 ml of deaerated USP phosphate buffer 7.2 (37±0.5°C). Filtered samples (0.45 μm) of 10 ml were withdrawn at different time intervals and were analysed spectrophotometrically (Pye Unicam, SP 6-550,England) at 318 nm (9).

For assessing the validity of the HPLC assay method (13) for stability testing, a standard solution of each drug was diluted with an equal volume of hydrogen peroxide (20 vol.) and the solution was left to stand for 48 hours of which a couple hours were in direct sunlight. The solution was finally assayed for drug content and the decomposition was found to be 100% indicating the validity of the assay method for stability testing.

Stability Testing

Uncoated and coated tablets were subjected to shelf-storage,in dark & at room temperature,for 11 months in tightly closed nylon bags. Twenty tablets from each

batch were weighed and powdered and an aliquot equivalent to two tablets was assayed for its drug content.

RESULTS AND DISCUSSION

From Table 1, it is clear that all the investigated tablets met the compendial requirements for uniformity of weight with relative standard deviation, RSD,(coefficient of variation) less than 0.5% which means excellent uniformity (14). The uniformity of thickness, inspite of being non-official, can be considered as an additional control to the tablet dimention and increased reproducibility. Table 1 obviates that all the prepared tablets had acceptable RSD of thickness uniformity (<6%) and were found to be parallel to those of weight. Indomethacin meglumine tablets were found to have the lowest RSD of weight and thickness, followed by indomethacin and indomethacin sodium tablets.

Regarding the mechanical properties of the prepared tablets, indomethacin meglumine tablets showed the highest hardness and the lowest friability values. Evaluation of the mechanical strength is better expressed by combining the hardness and friability in one figure to produce the hardness-friability ratio, HFR (15). It is clear from Table 1 that indomethacin meglumine tablets had the highest HFR, thus, reflecting excellent mechanical strength, while indomethacin sodium tablets had the lowest HFR.

For content uniformity, all the investigated tablets met the current compendial requirements, i.e., the amount of active ingredient in each of the 10 dosage units lies within the range of 85% to 115% and the RSD is less than or equal to 6% (9). In this study, the assay value of each of the 10 units is indeed within the range of 95% to 105% with a RSD not exceeds 1.51%

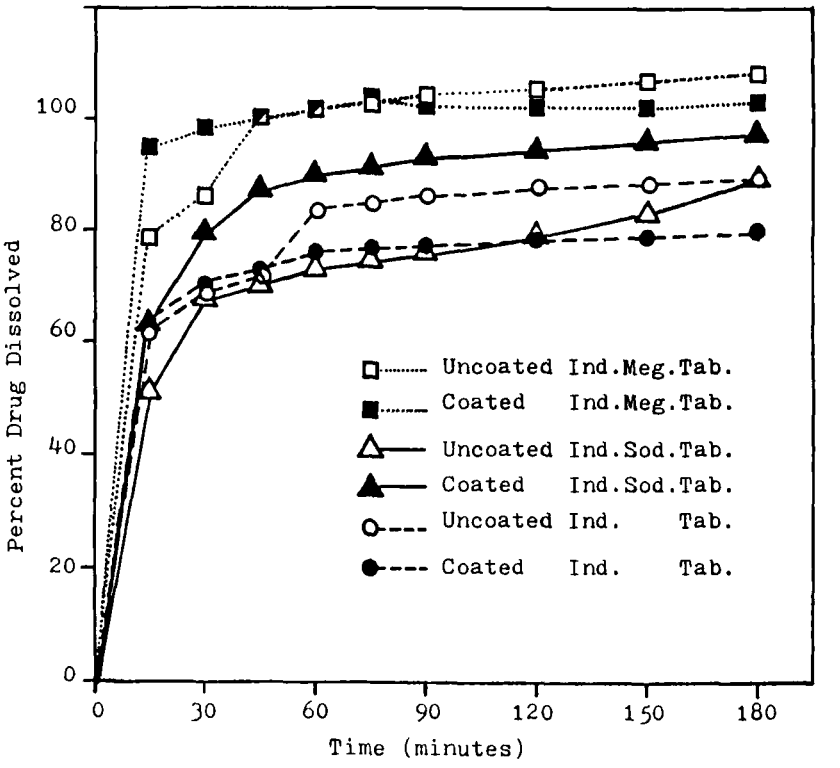

FIGURE 1

Dissolution profiles of uncoated and coated indomethacin, indomethacin sodium and indomethacin meglumine tablets.

(Table 1) or 2.3% if we consider the 95% two-sided upper confidence limit of RSD based on Method B (16),which means excellent uniformity and reflects a high degree of homogeneity of distribution of the active ingredient among the individual dosage units.

Figure 1 reveals that 68.64, 68.10 and 85.79 % of indomethacin and its sodium and meglumine salts were, respectively, dissolved from their uncoated tablets into the dissolution medium after 30 minutes, while the respective amounts dissolved from their coated tablets were 70.60, 79.72 and 98.56%. After 2 hours, the res-

pective amounts were 87.64, 79.69 and 105.89% for the uncoated tablets, and 78.6, 94.68 and 102.16% for the coated tablets. Comparing the aforementioned dissolution data with the compendial requirements (9) for indomethacin capsules (not less than 80% dissolved in 20 minutes) and for indomethacin extended-release capsules (80% in 2 hours), it is clear that indomethacin meglumine tablets, uncoated or coated, exhibited the best in-vitro release of its drug contents.

The results of the 11-months shelf-storing stability testing(Table 1) revealed that uncoated and coated indomethacin meglumine tablets were 100% stable, while those of indomethacin were fairly stable and those of indomethacin sodium were no more complied with the compendial requirements (9) for drug contents.

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