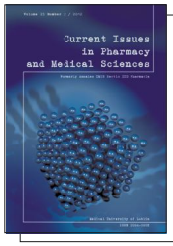

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Formulation and evaluation of sulfadimidine and trimethoprim tablets using wet granulation technique

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ABSTRACT

The objective of this study was to develop tablet formulations of sulphadimidine sodium (SDD-Na) and trimethoprim (TMP), evaluate and compare the efficiency of some excipients such as: superdisintegrant - croscarmellose sodium (Ac-Di-Sol), silicon dioxide (Aerosil), lactose and microcrystalline cellulose (Avicel pH-101) as base excipients for physical tablets properties and increasing the dissolution rate of SDD-Na and TMP. All tablet formulations were prepared by wet granulation process. Dissolution properties such as $DP_{30,45,60}$ (percent of drug dissolved at 30, 45 and 60 minutes), and dissolution rate constant value (K) were considered for comparing the dissolution results. The dissolution of SDD-Na and TMP from all examined tablet formulations followed Higuchi model kinetics with correlation coefficient (R) values from 0.984 to 0.995. The physical properties and in vitro drug release study revealed that tablets disintegration efficiency and drug dissolution depend on the amount of added disintegrant, the amount and presence of microcrystalline cellulose (Avicel) and lactose. Tablet formulation without addition of microcrystalline cellulose showed faster dissolution rate and shorter disintegration time as compared with that of tablets of formulations with microcrystalline cellulose. The results reveal that besides the type of diluents, the way of using superdisintegrant plays a major role in controlling disintegration of tablets. The portion of Ac-Di-Sol used as an intragranulary in the wet granulation process, is not as effective as that of the process of extragranulary addition. Tablets formulations F4 and F5 exhibited satisfactory friability, acceptable hardness, fulfilled the requirement for disintegration time for compressed tablets, and met the acceptable specifications with regard to drug release properties.

Keywords: dissolution, tablet excipients, sulphadimidine, trimethoprim, wet granulation, superdisintegrant

INTRODUCTION

The gastrointestinal tract provides sufficient fluid to facilitate disintegration of the dosage form and dissolution of the drug. The large surface area of gastric mucosa favors the drug absorption. Therefore, the oral route has continued to be the most appealing route for drug delivery, at least 90% of all drugs used to produce systemic effect are administered orally [6]. Solid dosage forms like tablets are the most popular and preferred drug delivery system. Tablet dosage forms are mainly composed of the drug and excipients such as a diluent, a binder, a lubricant, a disintegrant and a glidant [4]. The choice of formulation ingredients can have a significant effect on the rate and extent of drug dissolution [10].

Dissolution is essential for a drug to be absorbed through the biological membranes into systemic circulation for therapeutic efficacy. Conventional tablet formulations generally require rapid disintegration to aid drug dissolution. The simplest way to achieve quick disintegration is to use the superdisintegrant in connection with suitable diluents. Superdisintegrant such as croscarmellose sodium, is frequently used in tablet formulations to improve the rate and extent of tablet disintegration and thereby increase the rate of drug dissolution [16].

Drug dissolution testing of pharmaceutical products is a procedure used to evaluate drug release characteristics of solid oral products such as tablets and capsules and is a fundamental part of drug product development and manufacturing. Such testing confirms that a tablet has released the labeled quantity of active pharmaceutical ingredient (API) into solution within a designated time interval. It demonstrates that the API will be readily available for absorption after oral administration. The dissolution of the API in solid dosage forms is considered a key variable in the process of absorption in the gastrointestinal tract. The drug dissolution test is conducted using the basket, paddle methods or flow-through cell dissolution apparatus as described in compendia (USP, Eur. Ph., FP) [13].

Sulfonamides are a group of synthetic organic compounds with a broad spectrum against most gram-positive and gram-negative bacteria that have played an important role as effective chemotherapeutics in bacterial and protozoal infections in medicine and veterinary practice [2,11]. In clinical practice, sulfonamides administered individually or in mixtures, include sulfadiazine, sulfadimidine, sulfamethoxazole, sulfanilamide, and trimethoprim, which increase

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the power of sulfonamide [12]. They are used in treatment of otitis, bronchitis, sinusitis and pneumoystis pneumonia and urinary tract infections in combination with trimethoprim [8]. The most widely used veterinary antimicrobials in the European Union include tetracyclines, macrolides, penicillins, aminoglycosides and sulfonamides. In veterinary medicine, sulfonamides are widely used to treat animals as well as to enhance feed efficiency, promote animal growth and improve productivity. They cover infectious diseases of the digestive and respiratory tracts, secondary infections, mastitis, metritis and foot rot [1, 14].

Sulfadimidine is one of the most common sulfonamide antibacterials and widely used in veterinary medicine due to its effectiveness against a wide variety of diseases in food-producing animals such as necrotic pododermatitis in cattle, coccidiosis in sheep, bacterial pneumonia in pigs and so on [15].

The objective of this study was to develop tablet formulations of sulphadimidine sodium (SDD-Na) and trimethoprim (TMP), evaluate and compare the efficiency of some excipents such as: superdisintegrant – croscarmellose sodium (Ac-Di-Sol), silicon dioxide (Aerosil), lactose and microcrystalline cellulose (Avicel pH-101) as base excipient for tablet physical properties and increase the dissolution rate of SDD-Na and TMP.

MATERIALS AND METHODS

All chemicals were of analytical-reagent grade. Sulfadimidine sodium (SDD-Na) and trimethoprim (TMP) were purchased from POCH SA (Gliwice Poland). Lactose monohydrate, silicon dioxide, were purchased from Sigma Germany, Polivinylpyrrolidone K30 (PVP-K30) was obtained from Fluka. Microcrystalline Cellulose (Avicel PH-101) and superdisintegrant – croscarmellose sodium (Ac-Di-Sol), were gift samples from IMCD, (FMC Biopolymer, USA). Magnesium stearate used as internal lubricant was obtained from POCH SA (Gliwice Poland); ethanol was from P.P.H, „STANLAB".

The ammonium buffer solution pH 10 was prepared from POCH reagents. Ammonium hydroxide 25 % solution (HPLC grade) was obtained from POCH SA (Gliwice Poland).

The water was purified by Cobrabid-Aqua CA-ROD 3 ECO system.

Blending and Tableting. All tablets were prepared by wet granulation process. The tablet formulations: F1, F2, F3, F4 contained 80% of active substances and 20% of excipients and formulation F5 – 93.5% of active substances and 6.5% of excipients. The wetting agent was 1% PVP-K30 solution in (50:50 w/w) water/ethanol..

Tablet formulations: F1, F2, F3 were prepared by mixing SDD-Na and TMP with microcrystalline cellulose (Avicel pH-101), lactose and disaggregating agent (Ac-Di-Sol). The mixture was kneaded in the presence of an amount of 1% PVP-K30 solution in (50:50 w/w) water/ethanol and then extruded through a steel grid (1.0 mm). The final granulate was dried at 45^0°C and sieved. The granules were mixed with appropriate amounts of lubricant (magnesium stearate) and glidant (aerosil) (Formulation 3).

Tablets from formulation F4 were prepared by mixing SDD-Na and TMP with microcrystalline cellulose and lactose. The mixture was kneaded in the presence of an amount of 1% PVP-K30 solution in (50:50 w/w) water/ethanol and then extruded through a steel grid (1.0 mm). The final granulate was dried at 45°^{0}C and sieved. The granules were mixed with appropriate amounts of disaggregating agent (Ac-Di-Sol), lubricant (magnesium stearate) and glidant (aerosil).

Tablets from formulation F5 were prepared by mixing SDD-Na and TMP with disaggregating agent (Ac-Di-Sol). The mixture was kneaded in the presence of an amount of 1% PVP-K30 solution in (50:50 w/w) water/ethanol and then extruded through a steel grid (1.0 mm). The final granulate was dried at 45°^{0}C and sieved. The granules were mixed with appropriate amounts of lubricant (magnesium stearate).

The round flat-faced tablets were prepared on a single-punch tablet press (Erweka, EK-O) with 9.0 mm punches. The tablet press setting was kept constant across all formulations.

The tablets were evaluated for uniformity of weight, hardness, friability, drug content, disintegration time and dissolution properties.

Tablet properties. Tablets were tested for thickness and weight variation to determine any variability associated with the tablet press or the method of preparation.

The thickness was determined using digimatic caliper. Uniformity of mass was determined by weighing 20 tablets on an analytical balance (OHAUS Adventurer Pro) according to FP VI.

Measurement of friability. Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a friabilator (FP VIII) at 25 rpm for 4 minutes. The tablets were dedusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss. Friability below 1% is considered acceptable.

Hardness test. The hardness of six tablets was determined using an Erweka hardness tester (Type TBH 30, Erweka, Germany). The hardness coefficient was calculated from equation:

$$T = \frac{P_{\max}}{h \cdot d}$$

where: T – tablet hardness coefficient (kG/mm^2),
$P_{maks.}$ – tablet breaking force (kG),
d – tablet diameter (mm),
h – tablet thickness (mm).

All results are presented as mean value ± SD (n = 6). Hardness coefficient above 0.1 kG/mm^2 is considered acceptable.

Disintegration time. Respective disintegration times of the prepared tablets were measured in 900 ml of purified water with disks at 37°C using an ERWEKA tester (Type ZT 222, FP VIII). Disintegration time (n=6) was recorded until all the fragments of the disintegrated tablet passed through the screen of the basket.

Dissolution test. The dissolution profiles of SDD-Na and TMP were determined in a dissolution tester (Erweka Type DT 600 HH, Germany) following the (FP VIII, Eur. Ph. 7th edition) paddle method. All tests were conducted in 900 ml of purified water. The dissolution medium was maintained at a temperature of 37±0.5°0C with a paddle rotation speed at 100 rpm. At specified time intervals (5, 10, 15, 30, 45 and 60 min.), 2 ml of dissolution medium was withdrawn and replaced with an equal volume of purified water to maintain a constant total volume. The withdrawn samples were filtered through Whatman filter paper and SDD-Na and TMP content in each sample was analyzed after suitable dilution by first derivative spectrophotometric method at λ = 249 nm and λ = 268 nm [17]. A Thermo Scientific Helios Omega UV-VIS spectrophotometer connected to PC fitted with VISION pro software was used for all measurement and treatment of data. The drug content in each sample was calculated using calibration equations. Dissolution rate was studied for the prepared formulations.

Drug Content Estimation. The powder content of 10 tablets from each formulation was mixed well, and a powder sample equivalent to 250 mg of SDD-Na and 50 mg of TMP was placed in individual 100 ml volumetric flasks. Each drug was dissolved in 25 ml of ethanol. The resulting mixture was vortexed for 5 minutes, and the volume was raised to 100 ml with ethanol. The solution was filtered, and next a suitable dilution was analyzed for drug content by first derivative spectrophotometric method [17].

RESULTS AND DISCUSSION

SDD-Na and TMP tablets were successfully prepared and evaluated. The tablet formulations: F1, F2, F3, F4 contained 80% of active substances and 20% of excipients and formulation F5 93.5% of active substances and 6.5% of excipients. All tablet formulations were prepared by wet granulation process as given in Table 1. The portion of superdisintegrant (Ac-Di-Sol) was used as an intragranulary in tablet formulations: F1, F2, F3, F5 and extragranulary in formulation F4 at 2.5% concentration in tablet formulation F1 and 5% in tablets formulations: F2, F3, F4, F5. The humidity content in granulates was approximately 6%.

Table 1. Formulations of SDD-Na and TMP tablets

Formulation ingredients (mg/tablet)	Formula no.				
	F1	F2	F3	F4	F5
SDD-Na (active)	250	250	250	250	250
TMP (active)	50	50	50	50	50
Avicel PH- 101	37.5	37.5	37.5	37.5	–
Ac-Di-Sol (superdisintegrant)	9.38 (2.5%)	18.75 (5%)	18.75 (5%)	18.75 (5%)	16.2 (5%)
Lactose (filler)	22.5	13.125	9.375	9.375	–
Silicon dioxide	–	–	3.75	3.75	–
PVP 30	3.75	3.75	3.75	3.75	3.24
Magnesium stearate (lubricant)	1.875	1.875	1.875	1.875	1.62
Total tablet weight (mg)	375	375	375	375	324

The tablets were evaluated for uniformity of weight, hardness, friability, drug content, disintegration time and dissolution properties. Tables 2, 3 and 4, display the results.

The drug content of tablets was within the 100 ± 5% of label claim, and the results were satisfactory (Table 2). A good degree of uniformity of weight was achieved for all batches of prepared tablet formulations. The percent deviation did not exceed 5%, indicating excellent uniformity of weight in all the batches of prepared tablet formulations.

Table 2. Physical properties of prepared formulations of SDD-Na and TMP

Test	Results				
	F1	F2	F3	F4	F5
Mean weight (mg) (± % deviation)	375.5 (0.13)	367.3 (2.05)	377.6 (0.69)	379.5 (1.2)	327.0 (0.93)
Thickness (mm)	5.0±0.03	5.0±0.02	5.2±0.03	5.0±0.04	4.7±0.02
Hardness (kg/mm^2) ± SD	0.22±0.03	0.13±0.02	0.12±0.021	0.17±0.024	0.18±0.031
Friability (%)	0.26	0.3	1.07	0.88	0.36
Disintegration time (min)	41	24	21	11	9
Drug content:					
(%) SDD-Na	99.5	98.2	99.1	101.2	99.3
(%) TMP	97.8	99.2	102.3	98.3	101.8

The tablet batches exhibited good mechanical properties with regard to both hardness and friability except for formulation F3 with friability 1.07%. The hardness values were above 0.1 kG/mm^2 and within the batches of tablet formulations was from 0.12 (kg/mm^2) for formulation F3 to 0.22 (kg/mm^2) for formulation F1. In the friability studies, weight loss values of formulations: F1, F2, F4, F5 in the tablet batches was less than 1%.

The tablet formulations F4 and F5, fulfilled the FP requirement for disintegration time for compressed tablets: less than 15 minutes. The order of disintegration time of tablets formulations was: F1>F2>F3>F4>F5 (Table 2). The high disintegration time of tablet formulation F1 may be attributed to high hardness and relatively low amount of Ac-Di-Sol. The probable reason for higher hardness may be presence higher amount of lactose.

All tablet formulations were subjected to in vitro dissolution rate studies using purified water as the dissolution medium. Dissolution properties such as $DP_{30,45,60}$ (percent of drug dissolved at 30, 45 and 60 minutes), and dissolution rate constant value (K) were considered for comparing the dissolution results. The corresponding values for SDD-Na and TMP tablet formulations are given in Tables 3 and 4, and the dissolution profiles are shown in Figures 1 and 2. The results of dissolution studies indicate that dissolution rate of SDD-Na is increased in the following order: SDD-Na F2<F1<F3<F5<F4 and dissolution rate of TMP is increased in the following order: TMP F3<F2<F1<F4<F5.

Table 3. Dissolution parameters of SDD-Na from Tablet Formulations (n=6)

Formulation	DP_{30} (mean±SD)	DP_{45} (mean±SD)	DP_{60} (mean±SD)	$K(mg\ min^{-0,5})$
F1	53.31±2.75	71.78±2.71	84.06±2.12	30.375
F2	41.43±4.22	71.04±4.58	81.65±3.09	29.934
F3	55.39±3.38	71.28±1.34	77.73±4.04	26.720
F4	81.39±1.94	84.74±0.52	85.62±1.19	30.834
F5	78.82±5.40	83.78±1.38	84.10±3.24	34.820

$DE_{(30,45,60)}$ – percent of drug dissolved at 30, 45 and 60 minutes, K – Higuchi release rate constant

Table 4. Dissolution parameters of TMP from Tablet Formulations (n=6)

Formulation	DP_{30} (mean±SD)	DP_{45} (mean±SD)	DP_{60} (mean±SD)	K(mg $min^{-0,5}$)
F1	57.44±5.44	77.42±1.26	91.16±4,15	6.634
F2	50.74±4.06	79.72±3.51	90.24±5,90	6.357
F3	34.44±5.18	47.99±5	61.44±3,07	5.113
F4	72.55±2.10	87.13±1.79	91.92±4.01	6.887
F5	89.20±3.70	92.46±1.52	96.51±3.66	6.607

$DP_{(30,45,60)}$ – percent of drug dissolved at 30, 45 and 60 minutes, K – Higuchi release rate constant

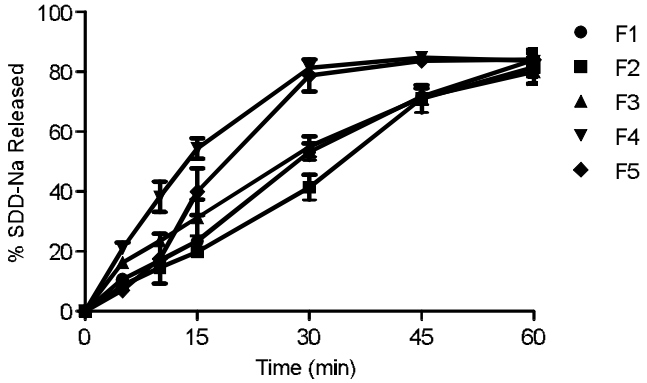

Fig. 1. In vitro release profiles of SDD-Na from Formulations: F1, F2, F3, F4, F5

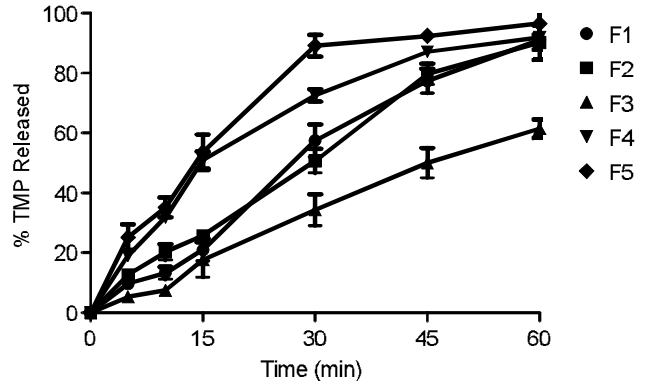

Fig. 2. In vitro release profiles of TMP from Formulations: F1, F2, F3, F4, F5

The dissolution of SDD-Na and TMP from all tablet formulations examined followed Higuchi model kinetics with correlation coefficient (R) values from 0,984 to 0,995 [3]. The Higuchi dissolution rate constant values, K (mg $min^{-0,5}$), are given in Tables 3,4 and are best for formulations F4 and F5.

To describe the kinetics of drug release, Higuchi's model was used [9,18].

$$Mt^* = K_0(\sqrt{t - \sqrt{T_D}}$$

Mt^* – amount of drug released in time t , release rate constant, square root of time, square root of dissolution lag time.
$\sqrt{T_D}$ – square root of dissolution lag time

The formulations F4 and F5 met the acceptable specifications with regard to drug release properties, that is, 80% of the drug was released within 45 minutes. Within 45 minutes 84.74% of SDD-Na for tablet formulation F4 and 83.78% for F5 were released, 87.13% of TMP dissolved from tablet formulation F4 and 92.46% from F5 in 45 minutes.

Tablet disintegration efficiency and drug dissolution depend on the amount of added disintegrant, the amount and presence of microcrystalline cellulose (Avicel) and lactose. Magnesium stearate concentration at 0.5% was quite sufficient to prepare tablets. Magnesium stearate decreases the wettability of the matrix and thus, may increase the disintegration time of a formulation. However, it was not evaluated if it might affect the compression ability of the formulation. The used wetting agent in all tablet formulations was 1% PVP-K30 solution in (50:50 w/w) water/ethanol. Generally, a binder increases the mechanical strength but delays dissolution time of tablet [5]. Concentration of lubricant and a binder should be selected as the independent variables for the experimental design [10].

The amount and presence of microcrystalline cellulose affects the disintegration time of tablets and release rate of drug. Tablet formulation F5 without addition of microcrystalline cellulose showed faster dissolution rate and shorter disintegration time as compared with that of tablets of formulations: F1, F2, F3, F4.

The results reveal that besides the type of diluents, the way of using superdisintegrant, plays a major role in controlling disintegration of tablets. Superdisintegrants are generally used for improvement of disintegration time dosage form and solubility for active pharmaceutical ingredients. Gordon et al. reported that Ac-Di-Sol used as intragranular disintegrant was relatively unaffected by wet granulation process but the portion of Ac-Di-Sol used an intragranulary in the wet granulation process in tablet formulation F3 is not as effective as that the process of extragranulary addition – formulation F4 [7]. In the wet granulation process the granules are exposed for wetting and drying, which reduces the properties of the disintegrant.

Extragranular incorporation produced faster results of the dissolution than in the case of an equal distribution intragranularly and extragranularly. In turn, it proved superior to intragranular incorporation.

CONCLUSIONS

Results of the present study demonstrate that tablets disintegration efficiency and drug dissolution depend on the amount of added disintegrant (Ac-Di-Sol), the amount and presence of microcrystalline cellulose (Avicel) and lactose. The results reveal that the disintegration time and percentage of dissolved drug were strongly influenced by the mode of addition of superdisintegrant. The dissolution of SDD-Na and TMP from all tablet formulations examined followed Higuchi model kinetics with correlation coefficient (R) values from 0,984 to 0,995. Tablet formulations F4 and F5 exhibited satisfactory friability, acceptable hardness, fulfilled the FP requirement for disintegration time for compressed tablets and met the acceptable specifications with regard to drug release properties.

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