2013 © Curr. Issues Pharm. Med. Sci. Vol. 26, No. 2, Pages 183-188

Current Issues in Pharmacy and Medical Sciences

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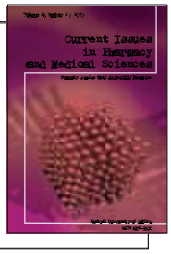

Release kinetics of sulfadimidine sodium and trimethoprim from tablets containing different excipients prepared by wet granulation method

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ABSTRACT

In this study seven tablet batches were prepared by wet granulation process using different excipients such as: superdisintegrant – croscarmellose sodium (Ac- Di- Sol), silicon dioxide (Aerosil), lactose, pregelatinized starch (CPharm Gel) and microcrystalline cellulose (Avicel pH- 101). Sulfadimidine sodium (SDD-Na) and trimethoprim (TMP) were used as model active substances. Tablets were evaluated for uniformity of weight, hardness, friability, drug content, disintegration time and dissolution properties. To study the release kinetics of the drugs, data obtained from *in vitro* drug release studies were plotted into the following kinetic models: zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas. The obtained results demonstrate that SDD-Na release kinetics was best described by Higuchi model followed by first order model. TMP release kinetics was best explained by first order model followed by Higuchi model. The Hixson-Crowell plot showed good linearity for SDD-Na and TMP. Release exponents values for Korsmeyer-Peppas model were characteristic for anomalous transport (non-Fickian) which appears to indicate a coupling of the diffusion and erosion mechanism or super case II transport refers mainly to the erosion of the polymeric chain.

Keywords: dissolution kinetics, kinetic models, tablet excipients, sulfadimidine sodium, trimethoprim, wet granulation

INTRODUCTION

Solid oral dosage forms remain the most convenient means of treatment. The effectiveness of these dosage forms relies on dissolution of a drug in gastrointestinal tract fluids before absorption into the systemic circulation. The rate of dissolution of a drug from a solid dosage form is therefore crucial for optimization of therapy [9]. Tablet dosage forms are mainly composed of the drug and excipients such as a diluent, a binder, a lubricant, a disintegrant and a glidant [1]. The choice of formulation ingredients has a significant effect on the rate and extent of drug dissolution [12].

Dissolution testing is therefore a useful tool for quality control as well as for formulation development, and is a regulatory requirement in the approval of new drug products [5,8,15]. Such testing confirms that a tablet has released the stated 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 [13].

In vitro dissolution is one of the most important elements of the drug development process. Several kinetic models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where *f* is a function of *t* (time) related to the amount of drug dissolved from the pharmaceutical dosage system [3].

The quantitative interpretation of values generated in dissolution studies is facilitated by the use of generic equation that mathematically translate dissolution curves as a function of some parameters related with the pharmaceutical dosage forms. In some cases, the equations can be deduced by a theoretical analysis of the processes to which a dosage form is subjected. Models that best describe drug release phenomena must be used to define drug release mechanisms as this helps to analyze and explain mathematically the processes that occur when a drug is released from a dosage form [4,9,10].

In this study, several mathematical models will be used to evaluate the release kinetics of the highly soluble

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DOI: 10.12923/j.2084-980X/26.2/a.14

sulfadimidine sodium (SDD-Na) and the poorly soluble trimethoprim (TMP) from the tablet batches prepared by wet granulation process by using the following excipients: superdisintegrant – croscarmellose sodium (Ac- Di- Sol), colloidal silicon dioxide (Aerosil), lactose monohydrate, pregelatinized starch (CPharm Gel) and microcrystalline cellulose (Avicel pH- 101).

MATERIAL 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 and colloidal silicon dioxide were purchased from Sigma, Germany. Polivinylpyrrolidone K30 (PVP-K30) was obtained from Fluka. Microcrystalline Cellulose (Avicel PH-101), pregelatinized starch (CPharm Gel) 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 purchased 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 using Cobrabid-Aqua CA-ROD 3 ECO system.

Blending and Tableting. All tablets were prepared by wet granulation process. The tablet batches: T1, T2, T3, T4, T6, T7 consisted of 80% of active substances and 20% of excipients. The total tablet weight was 375 mg.

Formulation T5 consisted of 93.5% of active substances and 6.5% of excipients. No fillers were used in the formulation T5. The total tablet weight was 321 mg. 1% PVP-K30 solution in water/ethanol (50:50 w/w) was used as wetting agent (Table 4).

Tablets: T1, T2, T3 were prepared by mixing SDD-Na and TMP with microcrystalline cellulose (Avicel pH-101), lactose and different amount (2.5 or 5%) of disaggregating agent (Ac-Di-Sol). The mixture was kneaded in the presence of an amount of 1% PVP-K30 solution in water/ethanol (50:50 w/w) and then extruded through a steel grid (1.0 mm). The final granulate was dried at 450°C and sieved. The granules were mixed with appropriate amounts of lubricant (magnesium stearate) and glidant (Aerosil) (T3).

The tablet batch T4 was 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 450°C and sieved. The granules were mixed with appropriate amounts of disaggregating agent (Ac-Di-Sol), lubricant (magnesium stearate) and glidant (Aerosil).

The tablet batch T5 was 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 450°C and sieved. The granules were mixed with appropriate amounts of lubricant (magnesium stearate).

The tablet batch T6 was prepared by mixing SDD-Na and TMP with pregelatinized starch and microcrystalline cellulose. 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 450C and sieved. The granules were mixed with appropriate amounts of disaggregating agent (Ac-Di-Sol) and lubricant (magnesium stearate).

The tablet batch T7 was prepared by mixing SDD-Na and TMP with pregelatinized starch 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 450°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. Formulation details of prepared tablets are presented in Table 4.

The dissolution profiles of SDD-Na and TMP were determined in a dissolution tester (Erweka Type DT 600 HH, Germany) by following the (FP IX, 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°C with a paddle rotation speed of 100 rpm. At specified time intervals (5, 10, 15, 30, 45 and 60 minutes), 2 ml of dissolution medium was withdrawn and replaced with an equal volume of purified water to maintain a constant total volume. The samples withdrawn were filtered through Whatman filter paper. The volume of samples was added to 25 ml volumetric flasks followed by 0.5 ml of ethanol, 5 ml of ammonium buffer solution (pH 10) and volume was adjusted with purified water. SDD-Na and TMP content in each sample was analyzed by first derivative spectrophotometric method at $\lambda = 249$ nm and $\lambda = 268$ nm [16].

The tablets were evaluated as per standard procedure for uniformity of weight, hardness, friability, drug content, disintegration time. The physical properties of prepared tablets and the drugs content are shown in the Table 5 [17].

Drug release kinetics. To study the release kinetics of the drug, data obtained from *in vitro* drug release studies were plotted in various kinetic models. Zero order (Eq. 1)

as the cumulative percentage of drug release *vs.* time. First order (Eq. 2), as the log of percent drug remaining to be released *vs.* time, Higuchi's model (Eq. 3), as cumulative percentage drug release *vs.* the square root of time and the Hixson-Crowell model as cube root of the initial drug concentration minus cube root of percent remaining *vs.* time (Eq. 4) (Fig.1, 2).

The zero order kinetics describes the systems where the drug release is independent of its concentration.

$$Q=K_0\,t \qquad \text{(Eq. 1)}$$

where Q is the amount of drug released in time t, K_0 is the zero order rate constant expressed in units of concentration [6].

The first order kinetics describes the release where release rate is concentration depended.

$$Log\ Q = Log\ Q_0 - Kt/\ 2.303 \qquad \text{(Eq. 2)}$$

where Q is the amount of drug released in time t, Q_0 is the initial amount of drug and K is the first order rate constant [2].

Higuchi's model describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion.

$$Q = K\,t^{1/2} \qquad \text{(Eq. 3)}$$

where Q is the amount of drug released in time t, K is the constant reflecting the design variables of the system [7].

To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data was also plotted using the Hixson-Crowell cube root law,

$$Q_0^{1/3} - Q_t^{1/3} = K_s t \qquad \text{(Eq. 4)}$$

where Q_t is the amount of drug remaining in time t in the tablet, Q_0 is the initial amount of the drug in the tablet, and K_s is the rate constant incorporating the surface–volume relation [3,4].

Mechanism of drug release. To evaluate the mechanism of drug release from tablets, data of drug release was plotted in Korsmeyer-Peppas equation (Eq. 5), as the log of cumulative % of drug released vs. log time, and the exponent n value was calculated through the slope of the straight line [11,14] (Fig 1, 2).

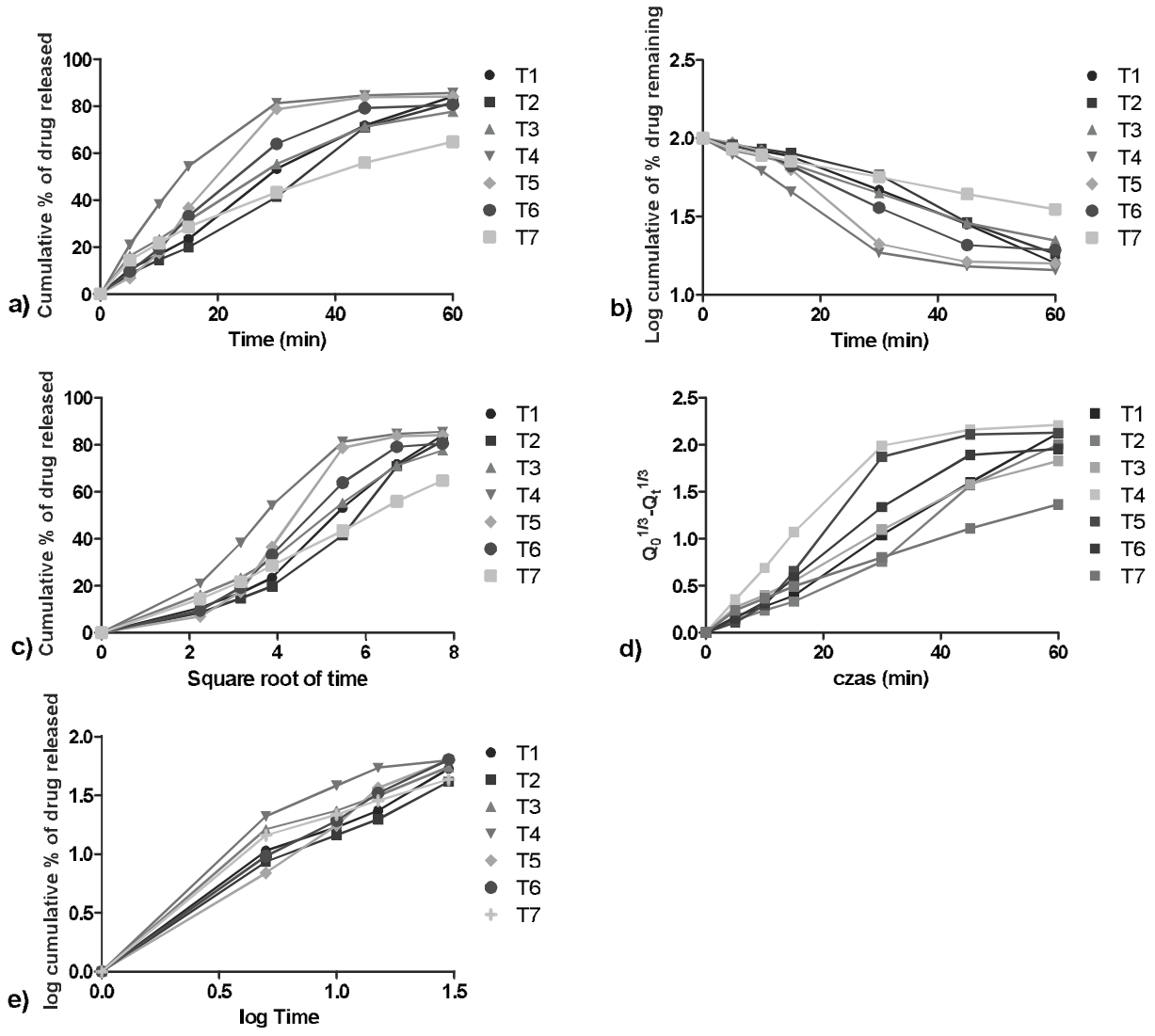

Fig. 1. Release kinetics of SDD-Na from prepared tablets: a. Zero order release profile, b. First order release profile, c. Higuchi release profile, d. Hixson-Crowell cube root plot, e. Korsmeyer-Peppas release profile

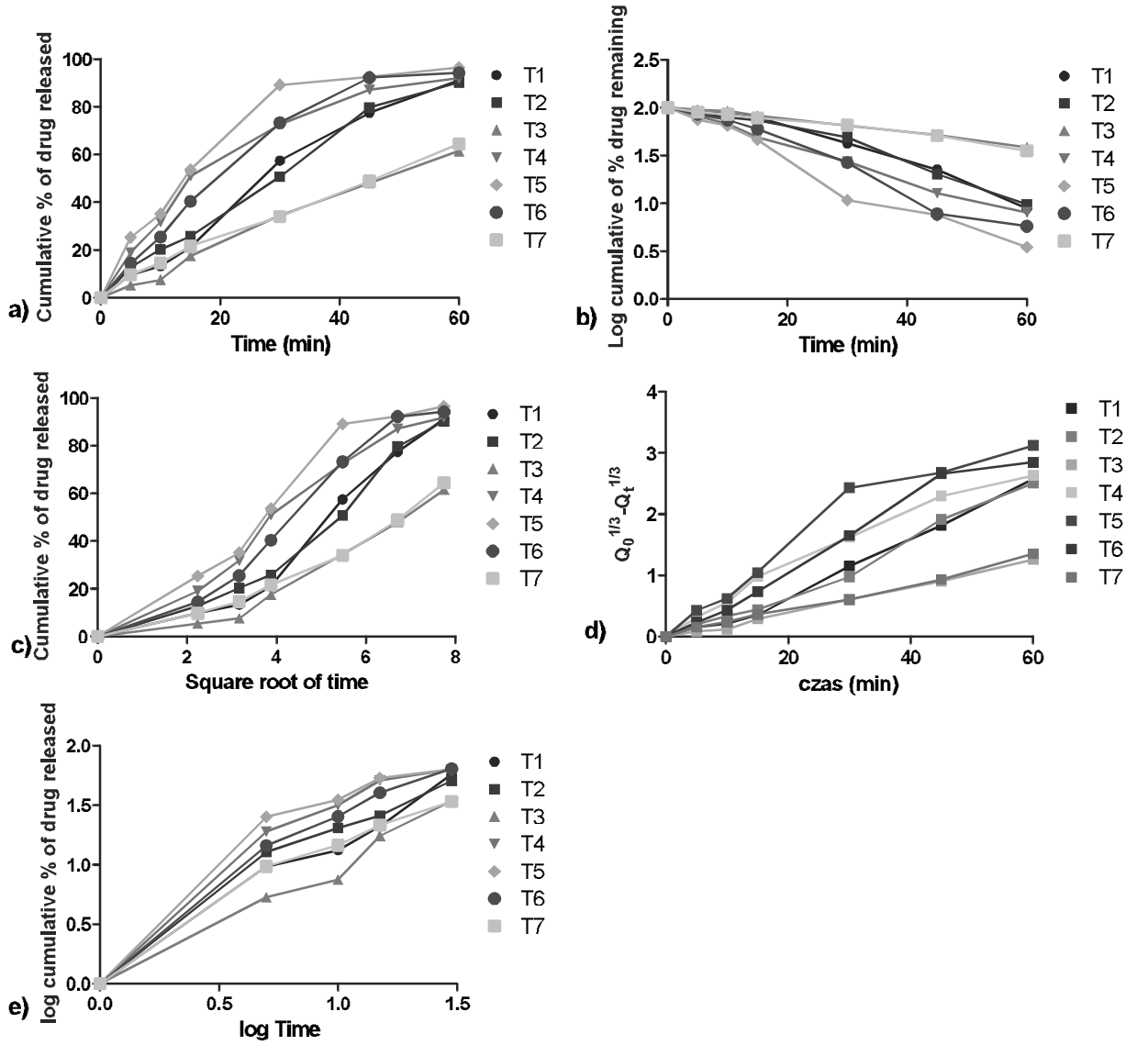

Fig. 2. Release kinetics of TMP from prepared tablets: : a. Zero order release profile, b. First order release profile, c. Higuchi release profile, d. Hixson-Crowell cube root plot, e. Korsmeyer-Peppas release profile

$$M_t / M\infty = Kt^n \qquad \text{(Eq. 5)}$$

Where $Mt/M\infty$ is the fraction of drug released at time t, K is a constant incorporating the properties of the macromolecular polymeric system and the drug. The n is an exponent used to describe the transport mechanism. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model [11].

Table 1. Drug transport mechanisms and diffusional exponents for cylindrical matrix tablets

Diffusional Exponent, *n*	Type of Transport	Time Dependence
0.45	Fickian diffusion	$t^{1/2}$
0.45 < *n* < 0.89	Anomalous transport	t^{n-1}
0.89	Case II transport	time independent
n > 0.89	Super case II transport	t^{n-1}

Kinetic analysis of dissolution data. The obtained drug release data were analyzed by zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas model. The release rate constants were calculated from the slope of the appropriate plot and coefficient of determination (r^2) was determined (Table 2, 3).

In this study, the *in vitro* release profiles of SDD-Na from tablet batches T1 and T3 were best explained by first order model as the plots showed the highest linearity (r^2=0.9909 and 0.9931), followed by Higuchi model (r^2=0.9858 and 0.9887) and 0 order (r^2=0.9808 and 0.9641).

The tablet batch T2 was best explained by zero order release kinetics as the plot showed the highest linearity (r^2=0.9856), which indicates that the concentration was nearly independent of drug release profile. The in vitro release profiles of SDD-Na from formulations: T4, T5, T6 and T7 showed best fit in Higuchi model (r^2= 0.8996 to 0.999), followed by first order kinetic model (r^2= 0.8797 to 0.995). However, for formulation T7, drug release was also found to be very close to zero order release (r^2= 0.9827).

Table 2. Dissolution kinetics of SDD-Na

Tabet batches	0 order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell	
	k	r^2	k	r^2	k	r^2	n	r^2	k	r^2
T1	1.408	0.9808	0.0319	0.9909	14.27	0.9858	0.8804	0.9893	0.0368	0.9965
T2	1.413	0.9856	0.0302	0.9717	14.16	0.9686	0.9477	0.9907	0.0356	0.9817
T3	1.173	0.9641	0.0253	0.9931	12.02	0.9887	0.6676	0.9917	0.0300	0.9874
T4	1.133	0.8002	0.0328	0.8797	12.14	0.8996	0.5728	0.9282	0.0348	0.8569
T5	1.487	0.8320	0.0362	0.8818	15.73	0.9119	1.0440	0.9329	0.0406	0.8665
T6	1.368	0.9099	0.0310	0.9585	14.25	0.9653	0.8858	0.9704	0.0358	0.9465
T7	0.911	0.9827	0.0161	0.9950	9.28	0.9990	0.6097	0.9990	0.0205	0.9967

Table 3. Dissolution kinetics of TMP

Tablet batches	0 order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell	
	k	r^2	k	r^2	k	r^2	n	r^2	k	r^2
T1	1.604	0.9749	0.0425	0.9752	16.23	0.9764	0.9958	0.9722	0.0456	0.9923
T2	1.493	0.9853	0.0404	0.9675	15.03	0.9769	0.8257	0.9896	0.0433	0.9844
T3	1.049	0.9865	0.0165	0.9950	10.58	0.9910	1.0450	0.9764	0.0218	0.9968
T4	1.314	0.9050	0.0430	0.9946	13.75	0.9688	0.6467	0.9664	0.0431	0.9780
T5	1.337	0.8466	0.0582	0.9656	14.12	0.9240	0.5838	0.9549	0.0517	0.9299
T6	1.533	0.9201	0.0537	0.9757	15.93	0.9712	0.7960	0.9789	0.0518	0.9699
T7	0.981	0.9983	0.0164	0.9809	9.823	0.9788	0.7629	0.9950	0.0212	0.9904

Table 4. Formulation details of kinetic model investigated tablets

Formulation ingredients (%)	Tablet batches						
	T1	T2	T3	T4	T5	T6	T7
SDD-Na	66.6	66.6	66.6	66.6	77.8	66.6	66.6
TMP	13.4	13.4	13.4	13.4	15.7	13.4	13.4
Avicel PH-101	10	10	10	10	-	6,75	-
Ac-Di-Sol	2,5	5	5	5 extragranulary	5	5 extragranulary	5
C Pharm Gel	-	-	-	-	-	6,75	15
Lactose monohydrate	6	3.5	2.5	2.5	-	-	-
Aerosil	-	-	1	1	-	-	-
PVP 30	1	1	1	1	1	1	1
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table 5. Physical properties of prepared tablets

Test	Results						
	T1	T2	T3	T4	T5	T6	T7
Mean weight (mg) (± % deviation)	375.5 (0.13)	367.3 (2.05)	377.6 (0.69)	379.5 (1.2)	324.0 (0.93)	374.0 (0.80)	373.0 (0.48)
Hardness (kg/mm^2) ± SD	0.22 ± 0.03	0.13 ± 0.02	0.12 ± 0.021	0.15 ± 0.024	0.12 ± 0.031	0.13 ± 0.052	0.19 ± 0.044
Friability (%)	0.26	0.3	1.07	0.88	0.36	0.85	0.29
Disintegration time (min)	41	24	21	11	9	14	23
Drug content (%) SDD-Na	99.5	98.2	99.1	101.2	99.3	97.9	98.5
(%) TMP	97.8	99.2	102.3	98.3	101.8	102.5	97.4

Uniformity of weight (n = 20), friability (n = 20), disintegration time test (n = 6) were determined according to FP IX and drug content test (n = 10) according to FP VI. Friability (%) = (loss in weight/initial weight) x 100

Hardness test (n = 6) was determined using an Erweka hardness tester (Type TBH 30). The hardness coefficient was calculated from equation:

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

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

The *in vitro* release profiles of TMP from formulation T1 showed highest linearity with the Higuchi model (r^2= 0.9764), followed by first order (r^2= 0.9752) and zero order (r^2=0.9749). Tablets batches: T3, T4, T5, T6 can be best explained by first order model as the plots showed best linearity (r^2= 0.9656 to 0.9950), followed by Higuchi model (r^2= 0.9240 to 0.9910) and zero order r^2=0.9865 for T3. This indicates that the release of drug from matrix is a square root of time dependent process describing the drug release rate relationship with concentration of drug. Tablet batches: T2 and T7 can be best explained by zero order release kinetics (r^2=0.9853 and 0.9983), which indicates that the drug release was nearly independent of its concentration.

The Hixson-Crowell plot showed good linearity r^2=0.9475 (0.8569 to 0.9967) for SDD-Na release and r^2=0.9774 (0.9299 to 0.9968) for TMP release indicated a change in surface area and diameter of the tablets with the progressive dissolution of the tablet as a function of time.

The obtained data was plotted into Korsmeyer-Peppas equation to learn about the confirmed diffusion mechanism. All tablet batches showed good linearity (r^2= 0.9282 to 0.999) with slope (n) values 0.573-1.044 for SDD-Na and 0,5838-1,045 for TMP release. For SDD-Na release, tablet batches: T1, T3, T4, T6 and T7 showed released exponents 0.6097 to 0.8858 characteristic of anomalous transport (non-Fickian) which appears to indicate a coupling of the diffusion and erosion mechanism. Tablet batches: T2 and T5 showed released exponents 0.9477

and 1.044 which indicates a super case II transport refers mainly to the erosion of the polymeric chain.

For TMP release, tablet batches: T2, T4, T5, T6 and T7 showed release dexponents 0.5838 to 0.8257 characteristic of anomalous transport (non-Fickian) and T1, T3 showed released exponents 0.9958 and 1.045 indicating a super case II transport. This indicates that SDD-Na and TMP release might have been controlled by more than one process.

CONCLUSIONS

Results of the present study demonstrate that SDD-Na release kinetics was best described by Higuchi model followed by first order model. TMP release kinetics was best explained by first order model, followed by Higuchi model.

Release kinetics of tablets with shortest disintegration time and extragranular Ac-Di-Sol addition or without diluents was best described by Higuchi (SDD-Na) or first order kinetic model (TMP). For formulations with longer disintegration time comprised of 15% pregelatinized starch or 10% microcrystalline cellulose and 3.5% lactose, drug release was found to be very close to zero order release. The Hixson-Crowell plots showed good linearity for SDD-Na and TMP release indicated a change in surface area and diameter of the tablets with the progressive dissolution of the tablet as a function of time.

Release exponent values for Korsmeyer-Peppas model were characteristic of anomalous transport (non-Fickian), which appears to indicate a coupling of the diffusion and erosion mechanism or super case II transport refers mainly to the erosion of the polymeric chain. The mechanism of release changed with the nature and contents of excipients in the tablet matrix and drug solubility. A coupling of the diffusion and erosion mechanism may indicate that drug release profiles were controlled by more than one process.

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