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STUDY OF EFFECT OF VARIOUS DISINTEGRANTS ON THE PHYSICAL PROPERTIES AND DISSOLUTION BEHAVIOR OF THE DIRECTLY COMPRESSED THEOPHYLLINE TABLETS

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الهدف من هذا البحث هو دراسة تأثير كفاءة بعض المفتتات في تركيزات صغيرة علي الصفات الطبيعية وسلوك انحلال الثيوفيللين من الاقراص المحضرة بالكبس المباشر، لقد تم استعمال خليط الافسيل بى أتش ١٠٢ مع الامكمبرس بنسبة وزنيه ١:١ فى صيغة الكبس المباشر لتحضير أقراص الثيوفيللين فى وجود أو عدم وجود المفتتات بعد الخلط المتجانس مع بعضهم فى خلاط تربيولا. وكانت المفتتات المستعملة هي أكديسول ، واكسبلوتاب ، وبولىبلاسيدون أكس ال١٠، والنشا ١٥٠٠ وقد استعملت في تركيزات صغيرة من ١ الى ٤٪. ولقد تم تقييم الصفات الطبيعية وسلوك انحلال أقراص الثيوفيللين المحضرة بالكبس المباشر طبقا لمواصفات دستور الأدوية الامريكى رقم ٢٣ لسنة ١٩٩٥. ولقد أظهرت كل الصيغ لاقراص الثيوفيللين خصائص ميكانيكية جيدة وطابقت المواصفات العيارية من حيث المحتوى الدوائى ودرجة الهشوشة. لقد أعطت كل صيغ الأ قراص التى تحتوى على المواد المفتتة زمن تفتت اسرع ومعدل انحلال أسرع من أقراص الثيوفيللين المرجعية ما عدا تلك التي تحتوى على النشا ١٥٠٠. لقد أعطت أقراص الثيوفيللين المرجعية زمن تفتت أطول يزيد عن ٣٠ دقيقة ومعدل انحلال بطئ، أي أنه لايطابق حدود دستور الأدوية الامريكى لاختبارى التفتت والانحلال للثيوفيللين. ولقد تمت دراسة حركية انطلاق الدواء من أقراص الثيوفيللين طبقا لمعادلة درجة الصفر ، ومعادلة الدرجة الأولى ومعادلة حركية انتشار الدواء. ووجد أن حركية انطلاق الدواء من أقراص الثيوفيللين المرجعية والتي تحتوى على اكسبلوتاب ، أو النشا ١٥٠٠ قد تبعت معادلة انتشار الدواء. بينما كانت حركية انطلاق الدواء من أقراص الثيوفيللين التي تحتوى على أكديسول، أو بولىبلاسيدون تتبع معادلة الدرجة الأولى.

The objective of this work was to study the efficiency of certain disintegrants in low levels on the physical characteristics and dissolution behavior of directly compressed tablets containing theophylline as a model drug. A directly compressible formula based on Avicel PH 102/Emcompress 1:1 weight ratio was used in the preparation of theophylline tablets after being efficiently mixed together in a turbula mixer with or without the addition of disintegrants. The used disintegrants namely were cross-linked carboxymethylcellulose sodium (Ac-Di-Sol), sodium starch glycolate (Explotab), crosspovidone (Polyplasidone XL10) and Starch 1500, in low concentrations from 1 to 4 %w/w. The physical properties and the dissolution behavior of the directly compressed theophylline tablets were evaluated according to USP XXIII (1995) limits. All the formulations of theophylline tablets showed good mechanical properties and complied with the standard requirements for uniformity of dosage units and friability. Directly compressed theophylline tablets without disintegrants (control) gave longer disintegration time which exceeds 30 min (outside the limits of USP), and slow dissolution rate. While the batches of tablets containing disintegrants exhibited rapid disintegration and faster dissolution rate except those tablets containing starch 1500. Mechanisms of the drug release were investigated from dissolution data of theophylline tablets according to zero-order, first-order and the matrix-diffusion controlled kinetics. The behavior of drug release from theophylline tablets (control) and those containing either Explotab or Starch 1500 occurred predominantly by diffusion mechanism, while the drug release from tablets containing either Ac-Di-Sol or Polyplasidone followed first-order kinetics.

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INTRODUCTION

A tablet dosage form contains a number of excipients, in addition to the active ingredients to assist in enhancing drug activity and acceptability of tablets to the consumers. It is, therefore, of vital importance to study the effects of these excipients such as binders, disintegrants and lubricants on tablet formulation. For most solid dosage forms, disintegration is a necessary first step for drug release from the tablet matrix. The use of disintegrants is common to enhance the rate of disintegration, thereby improving the drug release profile.[1] In recent years, some new materials, called superdisintegrants have been developed to improve the disintegration process. Sodium starch glycolate is the sodium salt of a relatively low substituted carboxymethylether of potato starch and is prepared by both crosslinking and substitution of potato starch. It is a widely used superdisintegrant in tablets prepared by both direct compression and wet granulation.[2]

Direct compression technique has some important advantages such as low labor input, being a dry process, and requiring fewest processing steps. Due to its advantages, direct compression will continue to expand as a preferred method of tablet manufacture for development of pharmaceutical solid dosage forms. Good mixing of excipients with active ingredients is necessary for reliable production of tablets with good uniformity of weight and drug content.

Theophylline is widely used as a bronchodilator for the treatment of asthma or obstructive pulmonary disease.[3] Anhydrous theophylline is taken as a model drug for ease of its spectrophotometric assay and because its solubility is not strongly pH dependent.[4] Anhydrous theophylline is sparingly soluble in water, and is erratically absorbed after oral administration.[5] It exhibits a potential bioequivalence problem owing to the non-reproducible rate of dissolution of the drug in gastrointestinal fluid.[6] Therefore, dissolution rate of theophylline from orally administered dosage forms should be studied attentively.

The objective of this work was to study the efficiency of certain disintegrants namely Ac-Di-Sol, polyplasidone XL10, Explotab, and starch 1500 in low levels from 1 to 4 %w/w on the physical characteristics and dissolution behavior of directly compressed tablets containing theophylline as a model drug. Another goal was to predict the mechanism of drug release from theophylline tablets in absence and presence of disintegrants.

MATERIALS AND METHODS

Materials

The following materials were used:

- Anhydrous theophylline USP XXII / BP.
- Avicel PH 102 NF (FMC corporation, Newark, DE, USA).
- Emcompress; dibasic calcium phosphate dihydrate (Mendell Co., Palterson, NY, USA).
- Ac-Di-Sol NF (FMC Corporation, Newark, DE, USA).
- Explotab NF/BP(sodium starch glycolate) (Mendell Co., Palterson NY, USA).
- Polyplasidone XL10 (crospovidone NF) which is cross-linked polyvinyl-pyrrolidone (GAF Chemicals corporation, Wayne NJ, USA).
- Starch 1500 which is Pregelatinized starch NF, (Colorcon,Inc., IP, USA).
- Magnesium stearate NF (Mallinckrodt Inc., St.Louis, Missouri, USA).

Equipment

The following equipment were utilized:

- Turbula mixer (Willy A. Bachofen AG Maschinemfabrick,Basel, Switzerland).
- Manesty tablet press (Manesty D3B, Manesty Machine Ltd., Liverpool, UK).
- Hardness tester (Key International Inc., model HT500)
- Hanson disintegration apparatus (Chatsworth, CA, USA).
- Friabilator (Pharma test, Italy).
- Dissolution tester (Pharma test, Italy).
- UV Spectrophotometer, Spectronic 601, Milton Roy Company, USA.
- Tablet Micrometer, (Mitutoyo Japan).

Methods

Preparation of theophylline directly compressed tablets

Accurate weights of anhydrous theophylline and Avicel PH 102/Emcompress 1:1 weight ratio were prepared and mixed

together in a turbula mixer for ten minutes. The disintegrant in 1-4 %w/w concentration was added along with the lubricant (1% of magnesium stearate) and mixed for further two minutes. Batches of 300 g of ingredients, as shown in the general formula of theophylline tablets (Table 1), were prepared and compressed at 1000 lbs into tablets with a mean weight of 300±5 mg using Manesty tablet press with 9 mm concave punches. Each tablet was targeted to contain 50 mg of theophylline. The produced tablets were collected and stored in tightly sealed bottles for subsequent evaluation according to USP XXIII requirements.

Evaluation of tablets

Weight variation

The uniformity of theophylline directly compressed tablets was determined according to weight variation test procedure described in the USP XXIII.[7] The mean and coefficient of variation percent, C.V.%, were calculated for 20 individually weighed tablets. USP acceptance criteria were applied in the evaluation of the results.

Tablet thickness and diameter

The thickness was measured individually for 10 tablets using Mitutoyo Micrometer. The thickness values were recorded in millimeters (mm), the mean and C.V.% were calculated. Also, the uniformity of diameter of tablets was determined by the micrometer and the mean of diameter was found to be equal to 9 mm.

Hardness

The hardness of theophylline tablets was measured using Key HT-500 hardness tester. The hardness of 10 tablets from each batch was recorded in kiloponds (kp), the mean and standard deviation were calculated.

Friability

The friability, resistance to abrasion, was measured for each batch using Pharma test friabilator. Twenty tablets were weighed and subjected to 100 rotations (25 rpm for 4 min) in the friabilator. The tablets were then freed of dust and re-weighed to determine loss due to abrasion. Friability is reported as the percent weight lost, and the mean of three determinations was calculated.

Disintegration time

Disintegration testing was performed on each tablet batch as described in the USP XXIII procedure. Six tablets from each batch were placed in a Hanson disintegration apparatus with distilled water (37±2°) as the immersion fluid The basket-rack assembly was allowed to ascend and descend at a constant frequency until complete disintegration of each six tablets was observed. The disintegration time of each tablet was recorded in minutes and the mean was calculated.

Dissolution studies

The dissolution test of the USP XXIII was utilized for theophylline directly compressed tablets. The USP paddle assembly (apparatus 2) rotating at 50 rpm was employed with 900 ml distilled water (37±0.5°) as the dissolution medium. Six tablets sampled from each batch, were accurately weighed and placed individually into the dissolution cups. At predetermined time intervals, 10 ml samples were withdrawn from each flask using a syringe, and were replaced by an equal volume of fresh dissolution medium kept at 37°. Concentration of the dissolved theophylline was determined spectrophotometrically at 272 nm, using a standard calibration curve of the drug. No interference from excipients with drug assay was noted. Dissolution studies were performed for all batches of directly compressed theophylline tablets, and the mean value of cumulative drug released from each of six tablets from each batch was calculated.

Kinetics of drug release

The dissolution data from different batches of theophylline tablets were analyzed according to:

Zero-order kinetics[8] using the equation;

$$M_t = M_o - k_o t \quad (1)$$

First-order mechanism[9] using the equation;

$$\text{Log}\,(M_o - M_t) = kt / 2.303 \quad (2)$$

Higuchi matrix diffusion controlled mechanism[10] using the equation;

$$M_t = kt^{1/2} \quad (3)$$

Where M_t is the amount of drug released at time t, and M_o is the initial drug loading, and k is a constant. Confirmation of the diffusion mechanism is provided by the logarithmic form

of an empirical exponential equation proposed by Ritger and Peppas[11] which is;

$$M_t/M_o = Kt^n \quad (4)$$

Where M_t/M_o is the fraction of drug released in time t, K denotes a constant incorporating structural and geometric characteristics of the tablets, and n is the release exponent indicating the type of drug release mechanism. According to equation 4, the drug release kinetics could follow: (1) Fickian diffusional release (if n = 0.5 in the case of slab) occurring by the usual molecular diffusion of drug due to a chemical potential gradient, or (2) case II relaxational drug release (if n = 1 in the case of slab) where the drug transport is associated with stresses and state transition in hydrophilic polymers which swell in water, or (3) anomalous non-Fickian transport (if $0.5 < n < 1$ in the case of slab).

RESULTS AND DISCUSSION

Table 1 shows the general formula for theophylline tablets prepared by direct compression technique. A directly compressible formula based on Avicel PH 102/Emcompress 1:1 weight ratio was used in this study, as it gave tablets of longer disintegration time (Table 2), which were taken as the control to study the action of certain disintegrants.

Table 2 demonstrates the physical characteristics of theophylline tablets containing various disintegrants in concentrations of 1-4 %w/w. It was found that theophylline tablets complied with the standard requirements of weight uniformity, as appeared from their low value of coefficient of variation percent and the mean weight was close to 300 mg, as targeted. Theophyline tablets passed the test for drug content uniformity according to the limits of USP XXIII, which claim that theophylline tablets should contain not less than 94 % and not more than 106 % of the labeled amount of anhydrous theophylline.[7]

From Table 2, the highest hardness value was obtained with directly compressed theophylline tablets containing polyplasidone XL10, which may be due to its different chemical nature (crospovidone). The concentration level of disintegrant from 1 to 4% showed almost no significant effect on hardness values probably due to the narrow range selected. Low values of standard deviation (SD) were obtained for hardness values of directly compressed theophylline tablets.

The friability of all batches of theophylline tablets showed very low values of weight loss % (< 0.2), as shown in Table 2 which indicates an excellent resistance to abrasion.

Regarding the disintegration test of theophylline directly compressed tablets, the control tablets showed longer disintegration time, (>30 min), while those containing various disintegrants gave shorter disintegration times except the batch containing 1% starch 1500, (>30 min). This may be due to rapid penetration of water into these tablets, and swelling, then disintegration. The disintegration time of theophylline tablets decreased with increasing the concentration of disintegrant. The efficiency of disintegrants can be arranged as Ac-Di-Sol > polyplasidone > Explotab > Starch 1500. This could be attributed to the higher swellability and moisture uptake of Ac-Di-Sol than polyplasidone, and modified starch, respectively.[12]

Figures 1-4 show the release profiles, in distilled water at 37°, of theophylline from directly compressed tablets containing Ac-Di-Sol, Explotab, Polyplasidone, and starch 1500, respectively, in comparison to the control. Slow dissolution rate of theophylline was obtained from the control tablets (about 50% released within two hours). The dissolution rate of theophylline from directly compressed tablets was increased by increasing the concentration of Ac-Di-Sol, Explotab, or polyplasidone, as compared to control, and reached to 100% of drug release within one hour. These results could be due to rapid disintegration of these tablets as observed before. These data revealed the efficiency of the disintegrants employed in low concentrations as exerted on the directly compressed tablets based on the blend of Avicel/Emcompress vehicles.

By increasing the concentration of starch 1500 from 1 to 4%, the dissolution rate of theophylline from its tablets was increased gradually than from the control one, (Fig. 4). The efficiency of starch 1500 in improving the release of theophylline was less than the other disintegrants used. This could be attributed to the longer disintegration time of theophylline tablets containing starch 1500, than other disintegrants, (Table 2).

Table 1: General formula for directly compressed theophylline tablets.

Ingredients	Amount per Tablet (mg)	Composition %w/w
Theophylline	50	16.67
Avicel:Emcompress (50:50)	247-235	82.33-78.33
Magnesium stearate	3	1
Disintegrant	3-12	1-4
Total	300	100

Table 2: The effect of various disintegrants on the physical characteristics of theophylline directly compressed tablets.

Disintegrants	Weight (g)		Thichness (mm)		Hardness (KP) Mean ± SD	Friability (% loss)	Disintegration time (min)
	Mean	C.V.%	Mean	C.V.%			
Control	0.2957	2.09	3.74	0.87	17.31±1.33	0.088	>120
Ac-Di-Sol 1%	0.2998	5.18	3.84	1.64	18.48±3.34	0.058	8.63
Ac-Di-Sol 2%	0.2975	2.45	3.88	1.34	16.83±1.74	0.052	0.93
Ac-Di-Sol 3%	0.2971	1.42	3.80	1.26	19.17±1.39	0.022	0.26
Ac-Di-Sol 4%	0.2992	1.96	3.83	1.27	18.97±1.21	0.003	1.03
Explotab 1%	0.3043	1.39	3.86	1.32	18.12±1.63	0.080	15.25
Explotab 2%	0.3008	1.44	3.85	1.36	18.78±0.95	0.086	1.86
Explotab 3%	0.2957	2.09	3.81	1.88	16.09±1.86	0.055	0.36
Explotab 4%	0.2923	2.84	3.87	0.73	17.03±2.57	0.072	1.74
Polyplasidone 1%	0.3027	1.91	3.88	0.98	20.22±1.33	0.082	26.36
Polyplasidone 2%	0.3013	2.12	3.90	1.02	20.86±1.86	0.092	1.38
Polyplasidone 3%	0.3011	1.28	3.86	0.48	21.33±1.31	0.017	0.37
Polyplasidone 4%	0.2997	1.00	3.92	1.15	21.00±2.01	0.042	0.14
Starch 1500 1%	0.2997	1.63	3.79	1.28	16.86±0.87	0.141	>30
Starch 1500 2%	0.3049	1.40	3.84	2.01	18.31±2.25	0.080	30
Starch 1500 3%	0.3013	0.87	3.85	1.27	17.64±1.38	0.093	29.09
Starch 1500 4%	0.2986	1.05	3.84	1.00	17.33±1.64	0.121	20.72

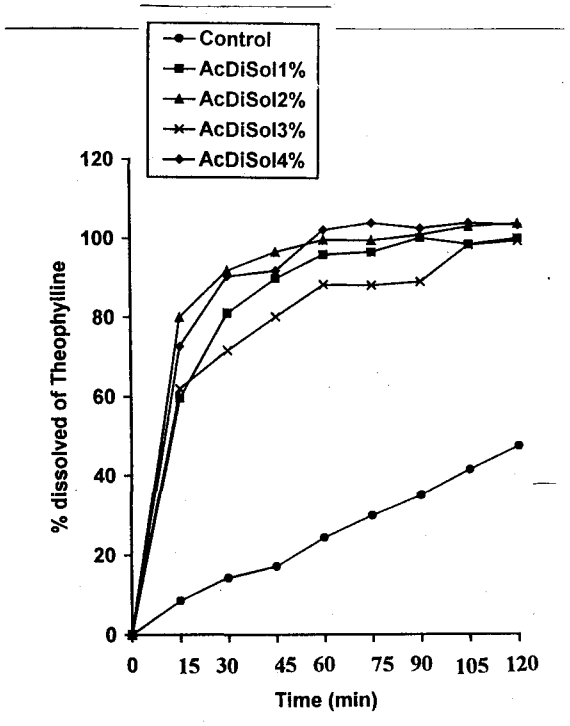

Fig. 1: Dissolution profiles of theophylline tablets containing Ac-Di-Sol 1-4% in water at 37°.

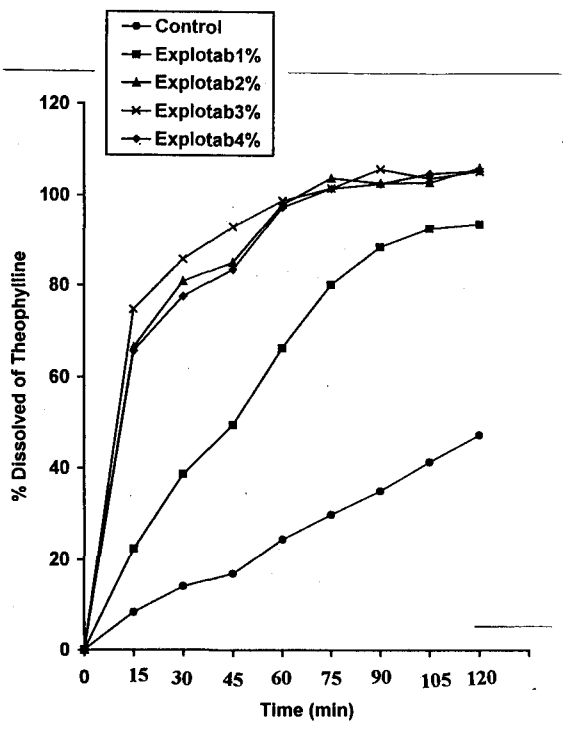

Fig. 2: Dissolution profiles of theophylline tablets containing Explotab 1-4% in water at 37°.

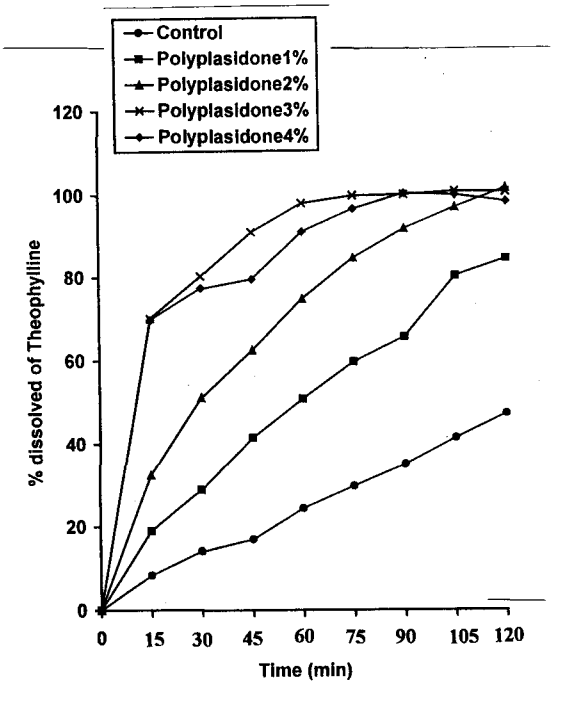

Fig. 3: Dissolution profiles of theophylline tablets containing polyplasidone 1-4% in water at 37°.

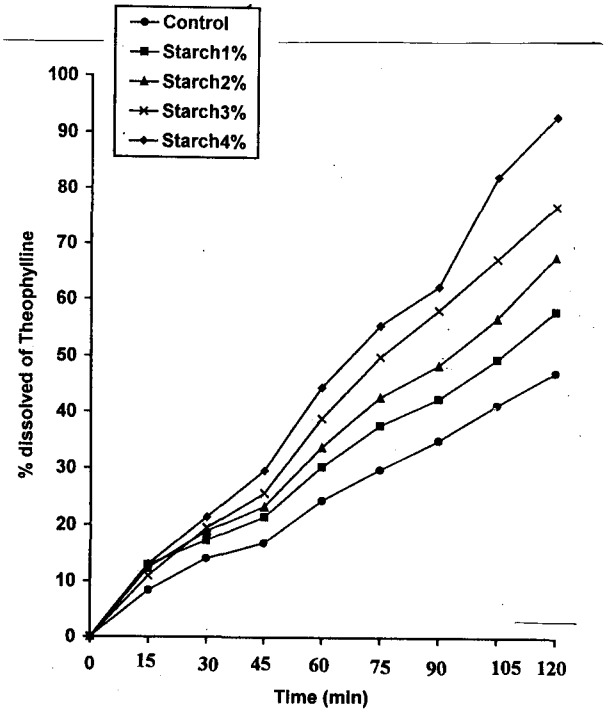

Fig. 4: Dissolution profiles of theophylline tablets containing starch 1500 from 1-4% in water at 37°.

USP XXIII claims that for the dissolution of theophylline tablets; not less than 80% of the labeled amount of anhydrous theophylline should dissolve in 45 min. As shown in Table 3, the batches which complied with these requirements are those containing Ac-Di-Sol (1-4%), Explotab (1-4%), Polyplasdone (2-4%) but not polyplasidone in 1%, starch 1500 in 1-4%, or the control. The efficiency of the studied disintegrants with respect to dissolution of theophylline tablets can be arranged in the following order: Ac-Di-Sol > Explotab > Polyplasidone > Starch 1500 > control. These results were confirmed also from their $T_{50\%}$, $T_{80\%}$, and relative dissolution rate (RDR) as shown in Table 3.

The results of drug release from theophylline tablets containing either Ac-Di-Sol or Polyplasidone acceptably followed first-order kinetics as verified by their high correlation coefficient fitting this order. Those theophylline tablets showed rapid disintegration and fast dissolution rate depending on the rapid permeation of water to tablets, which could be considered one of the reasons for fitting first-order of drug release.[13] On the other hand, the drug release from control theophylline tablets, and from those containing Explotab or Starch 1500 was found to fit predominantly the diffusion mechanism (either Higuchi diffusion model or Peppas diffusion model), as shown in Table 4.

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Table 3: The effect of various disintegrants in different concentrations on the dissolution profiles of theophylline directly compressed tablets.

Disintegrants	$T_{50\%}$	$T_{80\%}$	Relative dissolution rate RDR after (min)		
			15	30	60
Control	>120	>120	1	1	1
Ac-Di-Sol 1%	< 5	10	5.3	3.93	2.85
Ac-Di-Sol 2%	< 5	5	5.7	4.08	2.88
Ac-Di-Sol 3%	< 5	15	4.73	3.62	2.54
Ac-Di-Sol 4%	< 5	< 10	5.42	4.2	2.93
Explotab 1%	15	45	2.93	2.72	2.53
Explotab 2%	< 5	10	5.02	4.02	2.93
Explotab 3%	< 5	< 10	5.49	4.06	3.02
Explotab 4%	< 5	< 15	4.93	4.0	2.93
Polyplasidone 1%	30	90	2.45	2.09	1.87
Polyplasidone 2%	10	< 45	3.7	3.07	2.63
Polyplasidone 3%	< 5	10	5.4	4.03	2.83
Polyplasidone 4%	< 5	>15 < 30	4.7	3.75	2.87
Starch 1500 1%	90	>120	1.27	1.25	1.21
Starch 1500 2%	> 60 < 90	> 120	1.37	1.4	1.38
Starch 1500 3%	45	>120	1.51	1.6	1.66
Starch 1500 4%	>30 < 45	90	1.75	1.83	1.78

Table 4: Kinetic parameters calculated from dissolution data of theophylline from its directly compressed tablets containing different disintegrants.

Tablets contain	Zero-order		First-order		Diffusion model			
					Higuchi model		Peppas model	
	r	K_o mg/m	R (-)	$Kx10^{-3}$ min^{-1}	R	K_H $mg/m^{½}$	r	Slope (n)
Control	0.9720	0.324	0.9873	4.65	0.9985	4.42	0.9964	0.532
Ac-Di-Sol 1%	0.7962	0.551	0.9645	58.53	0.8679	6.07	0.9110	0.185
Ac-Di-Sol 2%	0.8400	0.668	0.9833	116.30	0.9029	5.66	0.9037	0.088
Ac-Di-Sol 3%	0.8814	0.349	0.9712	29.25	0.9388	4.37	0.9711	0.146
Ac-Di-Sol 4%	0.8914	1.007	0.9881	126.67	0.9357	8.33	0.9586	0.183
Polyplasidone 1%	0.9470	0.538	0.9920	14.26	0.9876	7.45	0.9867	0.459
Polyplasidone 2%	0.8830	0.518	0.9988	35.47	0.9530	7.43	0.9691	0.338
Polyplasidone 3%	0.8870	0.687	0.9834	87.97	0.9401	6.62	0.9720	0.167
Polyplasidone 4%	0.9732	0.582	0.9937	62.64	0.9910	5.99	0.9859	0.158
Explotab 1%	0.8755	0.574	0.9640	22.57	0.9497	8.27	0.9687	0.446
Explotab 2%	0.9366	0.822	0.9878	91.66	0.9741	7.78	0.9915	0.199
Explotab 3%	0.8890	0.588	0.9631	84.30	0.9420	5.66	0.9936	0.138
Explotab 4%	0.9481	0.846	0.9950	91.89	0.9821	7.98	0.9955	0.201
Starch 1500 1%	0.9760	0.381	0.9924	6.17	0.9988	5.18	0.9993	0.478
Starch 1500 2%	0.9762	0.461	0.9952	8.35	0.9987	6.26	0.9600	0.716
Starch 1500 3%	0.9635	0.555	0.9956	11.47	0.9961	7.62	0.9934	0.606
Starch 1500 4%	0.9797	0.682	0.9867	20.87	0.9990	9.23	0.9971	0.612

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