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RESEARCH PAPER

Effect of Fillers and Lubricants on Acetylsalicylic Acid Release Kinetics from Eudragit Matrix Tablets

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ABSTRACT

The effect of fillers and lubricants on the dissolution rate of acetylsalicylic acid (ASA) from matrix tablets has been evaluated. Eudragit S-100 and Eudragit L-100-55 where chosen as matrix substances. The process of drug release in vitro was studied by the modified half-change method. The dissolution data were evaluated on the basis of theoretical dissolution equations and by linear transformation of dissolution curves. Differences in release rate of ASA from matrix tablets, regarding the diluents used, appeared to be more significant when matrices contained Eudragit L-100-55 as compared to Eudragit S-100. The highest dissolution rates of ASA were observed in the presence of Lubritab as lubricant. The other lubricants used showed similar effects on the release rate of ASA. The release of ASA from samples containing Eudragit L-100-55 corresponded best to the zero-order kinetics. The best-fitted model for the ASA release from tablets prepared with Eudragit S-100 was obtained by using the Hixson–Crowell equation.

INTRODUCTION

Compressed matrices with dispersed active agent are the simplest approach in modified release form formulation. Acrylic polymers may be used as the basis for compressed matrices.

Many authors have described the prolonged release from acrylic polymer matrices (1–5). The most interesting among acrylic polymers were high-permeable Eudragit RL and low-permeable Eudragit RS. The Eudragits L-100-55 and S-100, widely used as enteric coatings, were rarely reviewed as release retardants. It was interesting to include both polymers in this study, as matrices for sustained-release acetylsalicylic acid (ASA) preparation, particularly because these polymers are directly compressible.

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Formulation additives modify the release rate from acrylic polymers matrices. Among other factors, the type and concentration of filler added influence the release rate of drugs (6–9). In general, the effect of replacement of acrylic polymers in the matrix by either a soluble or an insoluble filler, is an increase in dissolution rate of dispersed drug. The importance of the lubricant magnesium stearate for drug release from matrix tablets has been evaluated (10).

The purpose of the present investigation was to evaluate the behavior and effect of fillers and lubricants when added to a direct compression matrix formulation. Microcrystalline cellulose (Avicel pH 101), calcium sulfate (Compactrol), dextrose (Emdex), lactose (Fast-Flo Lactose), and calcium phosphate dibasic (Emcompress) were chosen as model fillers. Sodium stearyl fumarate (Pruv), hydrogenated cotton seed oil (Lubritab), glycerilbehenate (Compritol 888), and hydrogenated castor oil (Cutina HR) were chosen as model lubricants.

EXPERIMENTAL

Materials

In this study the following materials were used: acetylsalicylic acid (Röhm Pharma, Weiterstadt, Germany); Eudragit L-100-55 (Röhm Pharma, Darmstadt, Germany); Eudragit S-100 (Röhm Pharma, Darmstadt, Germany); Emdex (Mendell Co., New York, USA); Compactrol (Fluka AG, Buchs, Switzerland); Fast-Flo Lactose (Selectchemie AG, Zürich, Switzerland); Emcompress (Mendell Co., New York, USA); Avicel PH 101 (Fluka AG, Buchs, Switzerland); Precirol ATO 5 (Gattefossé, Saint Priest, France); Lubritab (Mendell Co., New York, USA); Pruv (Mendell Co., New York, USA); Compritol 888 ATO (Gattefossé, Saint Priest, France); Cutina HR (Henkel, Düsseldorf, Germany); Aerosil 200 (Degussa AG, Frankfurt, Germany); talc (Zorka, Šabac, Yugoslavia).

Methods

Samples

Nine different samples, each containing 325 mg of ASA, were prepared and designated as samples type L, corresponding to Eudragit L-100-55, used as matrix substance. Another nine samples were prepared and designated as samples type S, corresponding to Eudragit S-100, used as matrix for tablet making.

Samples type L: Samples L_1 to L_5 have 12.75% of different fillers and 1% of Precirol ATO 5 as lubricant; samples L_6 to L_9 have 1% of different lubricants.

Samples type S: Samples S_1 to S_5 have 12.75% of different fillers and 1% of Precirol ATO 5 as lubricant; samples S_6 to S_9 have 1% of different lubricants.

The composition of samples is presented in Table 1.

Preparation and Characteristics

Tablets were prepared by the direct compression method. Tablets weighting 400 mg were compressed on a single-punch tablet machine (EKO Korsch, Berlin, Germany) using 9-mm flat-face punches. The compression force was adjusted so that corresponding crushing strengths of tablets were between 10 and 15 kg.

Weight variations were determined according to Ph. Jug. IV. Crushing strength was determined by using the hardness tester (Erweka TB 24, Hausenstamm, Germany) with six individual tablets. Friability was calculated after rotation of 10 tablets for 5 min at 20 rpm in a friabilator (Erweka TA 3, Heusenstamm, Germany).

Content of ASA and free salicylic acid (SA) was determined by the third-order derivative spectrophotometric method (11). The ultraviolet (UV)–visible spectrophotometer GBC (Model 914, GBC Scientific Equipment, Dandendong, Australia) was used. The corresponding amplitudes $D_{269.09}$ for ASA and D_{320} for SA were measured. Dissolution rate of ASA was determined by using an Erweka apparatus (Erweka DT 6, Heusenstamm, Germany) with rotating basket. The temperature of the testing medium was 37° ± 0.5°C. The stirring speed was 50 rpm. The method of dissolution rate investigation was the modified half-change method (12). The pH change of the testing medium was as follows: after 0–1 hr of investigation, pH was 1.2; after 1–2 hr 6.2; after 3–4 hr 6.9; after 4–5 hr 7.2; after 5–6 hr 7.3; after 6–7 hr 7.4; after 7–8 hr 7.5. The subsequent test medium at each point was obtained by removing half of the previous medium and by adding the corresponding quantity of artificial intestinal juice. The samples taken from the test medium at given intervals were filtered through a membrane filter (0.22 μm) and dissolved ASA was assayed spectrophotometrically at 278 nm for samples having pH 1.2; at 276 nm for samples having pH 2.0; and at 268 nm for samples having pH 6.2–7.5. The apparatus used was the same as in content determination.

Table 1

Matrix Tablets Type L Formulated with Eudragit L-100-55[a]

Formulation	Milligrams Raw Material Per Tablet								
	L_1	L_2	L_3	L_4	L_5	L_6	L_7	L_8	L_9
ASA	325	325	325	325	325	325	325	325	325
Eudragit L-100-55	12	12	12	12	12	12	12	12	12
Emcompress	51								
Avicel PH 101		51				51	51	51	51
Compactrol			51						
Emdex				51					
Fast-Flo Lactose					51				
Precirol ATO 5	4	4	4	4	4				
Lubritab						4			
Pruv							4		
Compritol 888 ATO								4	
Cutina HR									4
Aerosil 200	2	2	2	2	2	2	2	2	2
Talc	6	6	6	6	6	6	6	6	6

[a]Matrix tablets type S have the same composition except that Eudragit S-100 is used instead of Eudragit L-100-55.

Release Kinetics

After linear transformation of dissolution curves, the results were tested with the following mathematical models:

- The zero-order equation assumes that drug release is constant:

$$M = M_0 - k_0 t \quad (1)$$

In this equation M is the amount of drug remaining undissolved at time t, M_0 is the amount of drug undissolved at $t = 0$, and k_0 is the corresponding release rate constant.

- Release behavior generally follows the following first-order release equation:

$$\ln M = \ln M_0 - k_f \cdot t \quad (2)$$

where M is the amount of drug undissolved at time t, M_0 is the amount of drug undissolved at $t = 0$, and k_f is the corresponding release rate constant.

- The Hixon–Crowell cube root equation is:

$$\sqrt[3]{M} = \sqrt[3]{M_0} - K_C \cdot t \quad (3)$$

where K_C is the cube root dissolution rate constant.

- A form of the Higuchi square root law (diffusion model) is given by equation:

$$Q = k_s \cdot \sqrt{t} \quad (4)$$

where Q ($Q = 100 - M$) is the amount of drug dissolved at time t and k_S is the corresponding rate constant.

In this work, Eqs. (1)–(4) were used.

RESULTS AND DISCUSSION

The characteristics of samples type S and L are described in Tables 2 and 3, respectively.

Weight variation All our results complied with the specified limitations of the number of test tablets that may lie outside certain limits (Ph. Jug. IV).

Crushing strength The desired value of crushing strength was 10–15 kg. The investigation showed that samples corresponded to these values, except in the case of samples S_4 and L4, which had crushing strengths of 9.43 and 9.15 kg, respectively.

Friability The values of friability were acceptable with the exception of sample S_4, where this value was higher than 1.0%.

Table 2

Characteristics of Acetylsalicylic Acid Matrix Tablets Type S

Sample	Mean Weight (g)	ASA Content (%)	SA Content (%)	Friability (%)	Crushing Strength (kg)
S_1	0.4005	95.20	0.291	0.51	11.10
S_2	0.3962	96.86	0.266	0.29	11.23
S_3	0.3996	100.74	0.200	0.45	9.43
S_4	0.3938	95.71	0.130	1.76	10.82
S_5	0.3972	98.68	0.180	0.47	10.83
S_6	0.4026	95.07	0.282	0.33	12.14
S_7	0.4035	98.08	0.264	0.32	11.27
S_8	0.3983	96.16	0.240	0.31	12.13
S_9	0.4073	110.59	0.242	0.30	11.61

Content of acetylsalicylic acid and salicylic acid The acetylsalicylic acid contents fell outside given limits in the following samples: sample S_9 (110.59%), sample L_4 (94.30%), and sample L_5 (94.37%). Other investigated samples had acceptable ASA content.

According to USP XXII, the content of SA could be up to 3%, compared with declared ASA content, in the case of prolonged-release ASA formulations. All our results for SA content were significantly lower in comparison with the limitation of USP XXII.

Dissolution test Figures 1 and 2 summarize the results of dissolution tests of ASA from samples type S and L when test media with pH value moving from 1.2 to 7.5 (half-change method) were applied. The effects f five different fillers on the release profile of ASA from matrix tablets are presented.

Change of filler does not significantly influence the dissolution rate of ASA (Fig. 1) during the first 2 hr of investigation. Slightly higher dissolution rate was noticed only for sample S_2, containing Avicel PH 101 as a filler, probably because Avicel PH 101 strongly attracts water. Only in tablets containing Avicel PH 101 (sample S_2) was the effect of fast swelling (immediately after immersion of matrix tablet in test medium) visible. A higher dissolution rate of ASA was observed for sample S_2 compared to other samples during the whole experiment. After 8 hr 71.9% of ASA had been dissolved from sample S_2.

It could also be observed from Fig. 1 that among four other samples, those containing water-soluble fillers (S_4 and S_5) released the drug faster than those containing water-insoluble fillers (S_1 and S_3). This is probably because water-soluble fillers are readily dissolved

Table 3

Characteristics of Acetylsalicylic Acid Matrix Tablets Type L

Sample	Mean Weight (g)	ASA Content (%)	SA Content (%)	Friability (%)	Crushing Strength (kg)
L_1	0.4035	96.18	0.185	0.05	10.60
L_2	0.4040	98.00	0.117	0.10	10.27
L_3	0.3994	94.30	0.140	0.37	9.15
L_4	0.4007	94.37	0.112	0.48	10.38
L_5	0.4005	95.41	0.168	0.49	11.56
L_6	0.4046	99.69	0.130	0.26	12.51
L_7	0.4011	100.45	0.098	0.23	11.12
L_8	0.4049	100.19	0.092	0.22	12.36
L_9	0.4051	97.07	0.096	0.27	12.87

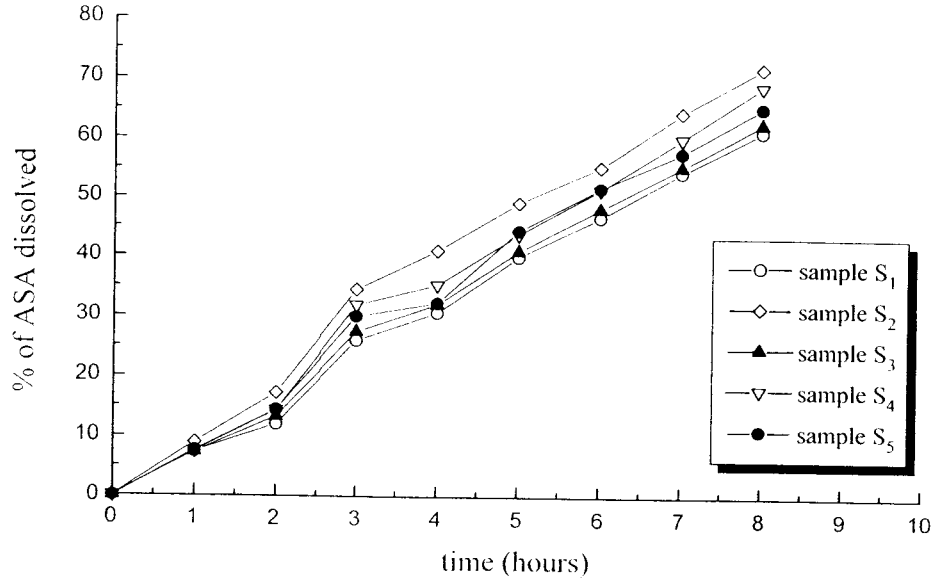

Figure 1. Dissolution profiles of ASA matrix tablets type S prepared with different fillers.

and by leaving the matrix act as channeling agents. The differences between dissolution rates of ASA from samples prepared with water-soluble and water-insoluble fillers are small.

Figure 2 shows dissolution rates of ASA from samples type L. The samples investigated were of the same composition as samples type S (Table 1) except that Eudragit S-100-55 was replaced with Eudragit L-100.

Drug release from samples type L was faster than from samples type S, and the total quantitity of ASA dissolved after 8 hr was greater. But different extents of increase of ASA dissolved were observed. By comparing the corresponding samples type L and S, it could be

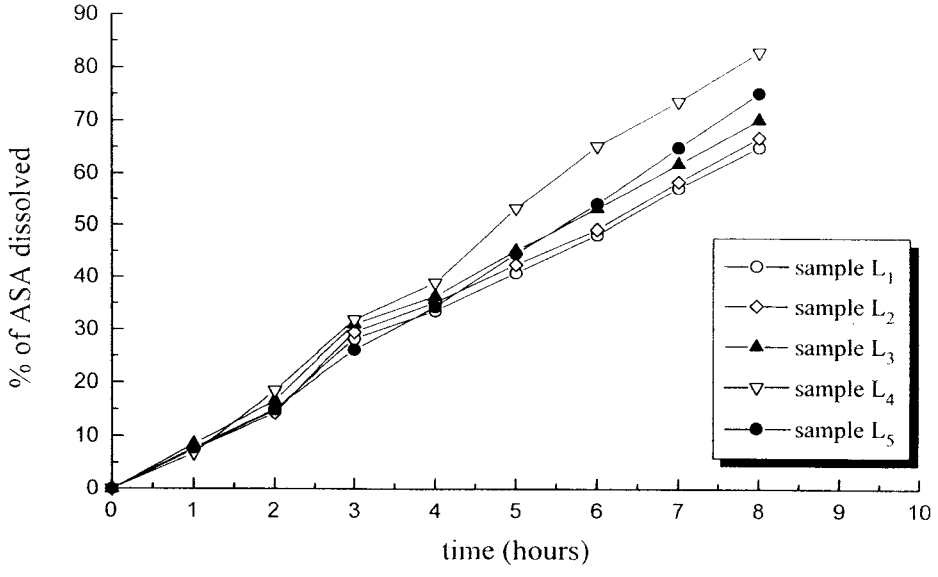

Figure 2. Dissolution profile of ASA matrix tablets type L prepared with different fillers.

seen that percent of ASA dissolved from sample L_1 after 8 hr was greater than from sample S_1, by only 3.68%. Samples L_1 and S_1 have the same water-insoluble filler (dibasic calcium phosphate dihydrate—Emcompress). On the other hand, the difference between percent of ASA dissolved from samples S_4 and L_4 was 14.04% (both samples were prepared with the water-soluble filler Emdex).

This may be due to the fact that the dissolution of Eudragit L-100-55 starts at pH 5.5, prior to the dissolution of Eudragit S-100, under the conditions of our experiment. Dissolved Eudragit L-100-55 polymer causes earlier erosion of matrix tablet than in the case of Eudragit S-100. As the tablet erodes, aqueous test medium penetrates into the matrix structure and dissolves water-soluble filler. The dissolved filler moves off the matrix, leaving the void space and increasing tablet porosity. These conditions lead to increase of ASA release from matrix.

It is interesting that dissolution rate from sample L_2 was lower than from sample S_2, both prepared with Avicel PH 101 as a filler. The possible explanation is that there is the competition for water between polymer Eudragit L-100-55 and Avicel PH 101. Avicel PH 101 readily absorbs water and the dissolution of polymer is retarded, which affects the dissolution rate of ASA.

Figure 3 shows the dissolution rate of ASA from samples type S prepared with Eudragit S-100 as polymer, Avicel PH 101 as filler, and different lubricants. The release rates of all samples were very close during the first 3 hr of investigation. After the third hour, the release rates of ASA from samples S_8 and S_9, prepared with the hydrophobic lubricants Compritol 888 and Cutina HR, were almost identical.

The release rate and dissolved quantity of ASA after 8 hr had the highest values in the case of sample S_6, prepared with Lubritab as lubricant. The percent of ASA released from sample S_6 after 8 hr was 80.30%. This was somewhat unexpected because it is known that Lubritab itself could be used as hydrophobic retarding substance in prolonged preparations (of course, in higher quantities).

It is interesting that Pruv, being a hydrophilic lubricant, did not affect the increase in percent of ASA dissolved from sample S_7. On the contrary, percent of ASA released was decreased compared to release from samples S_6, S_8, and S_9. But the solubility of Pruv is rather low (0.005 g of Pruv is dissolved in 100 g of water).

Figure 4 shows the dissolution rate of ASA from four samples type L prepared with different lubricants and with Eudragit L-100-55 as a polymer. By comparing the results in Figs. 3 and 4 it could be concluded that percent of ASA released from samples type L was lower than from samples type S. From sample S_6, prepared with Lubritab, after 8 hr 68.31% of ASA was dissolved, the highest value among four investigated matrix tablets type S. A very low percent of released ASA from

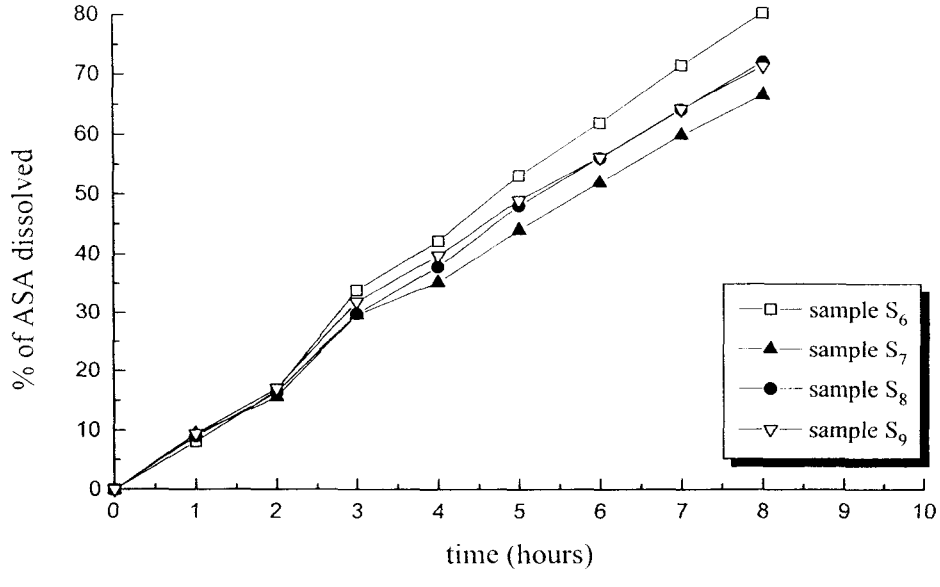

Figure 3. Dissolution profile of ASA matrix tablets type S prepared with different lubricants.

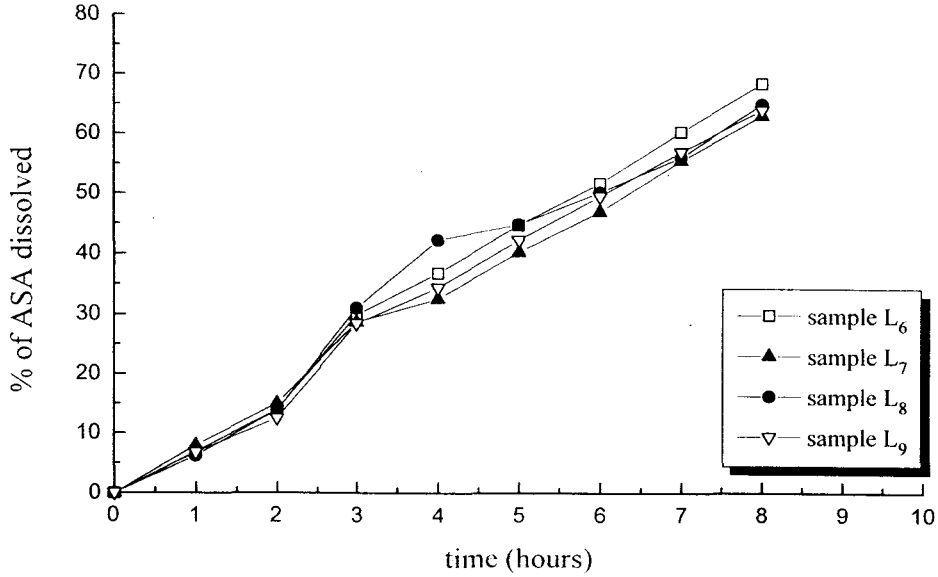

Figure 4. Dissolution profiles of ASA matrix tablets type L prepared with different lubricants.

sample S_7, prepared with Pruv as lubricant, was observed.

In Table 4 the kinetic parameters for ASA release from matrix tablets type L are presented. The release pattern of ASA from samples type L corresponded best to the zero-order kinetics. The only exception was sample L_8, where it was not possible to find a high correlation coefficient for any kinetics.

The results presented in Table 5 indicated that for sample type S, the best linearity was achieved using the Hixson–Crowell equation. Quite high correlation coefficients were obtained with other kinetic models. The differences between these models were noted to be minimal.

CONCLUSIONS

Water-soluble fillers enabled better penetration of test medium into the matrix and enhanced the release of

Table 4

Kinetic Parameters for Acetylsalicylic Acid Release from Matrix Tablets Type L

	Zero-Order Kinetics		First-Order Kinetics		Cube Root Equation		Diffusion Model	
Sample	r	k (% h^{-1})	r	k (h^{-1})	r	k (% $^{1/3}h^{-1}$)	r	k (% $h^{-1/2}$)
L_1	0.9968	8.0998	0.9909	0.1349	0.9953	0.1749	0.9922	31.4256
L_2	0.9950	8.3648	0.9902	0.1417	0.9946	0.1826	0.9923	32.5201
L_3	0.9967	8.7254	0.9904	0.1556	0.9957	0.1968	0.9934	33.0023
L_4	0.9980	10.9886	0.9807	0.1243	0.9925	0.2775	0.9928	42.6077
L_5	0.9992	9.7130	0.9767	0.1813	0.9882	0.2251	0.9852	37.3223
L_6	0.9967	8.7500	0.9934	0.1508	0.9932	0.1930	0.9943	34.1080
L_7	0.9956	7.7350	0.9918	0.1263	0.9952	0.1650	0.9921	30.0444
L_8	0.9767	7.7195	0.9894	0.1340	0.9876	0.1742	0.9897	32.0327
L_9	0.9943	8.2509	0.9956	0.1353	0.9970	0.1764	0.9935	32.1688

Note. r = correlation coefficient.

Table 5

Kinetic Parameters for Acetylsalicylic Acid Release from Matrix Tablets Type S

Sample	Zero-Order Kinetics		First-Order Kinetics		Cube Root Equation		Diffusion Model	
	r	k (% h^{-1})	r	k (h^{-1})	r	k (% $^{1/3}h^{-1}$)	r	k (% $h^{-1/2}$)
S_1	0.9960	7.8693	0.9939	0.1254	0.9964	0.1652	0.9904	30.5017
S_2	0.9912	8.9019	0.9935	0.1638	0.9963	0.2048	0.9952	34.8415
S_3	0.9958	7.9539	0.9946	0.1288	0.9970	0.1687	0.9926	30.9061
S_4	0.9927	8.6421	0.9886	0.1501	0.9932	0.1916	0.9908	33.6216
S_5	0.9924	8.2629	0.9966	0.1386	0.9975	0.1792	0.9952	32.3028
S_6	0.9961	10.4168	0.9871	0.2145	0.9967	0.2566	0.9950	40.5615
S_7	0.9966	8.3061	0.9943	0.1428	0.9973	0.1832	0.9930	32.2605
S_8	0.9976	9.1644	0.9929	0.1678	0.9976	0.2102	0.9941	35.5982
S_9	0.9950	8.9530	0.9956	0.1638	0.9985	0.2053	0.9959	34.9298

Note. r = correlation coefficient.

ASA from samples. The effect of fillers on the release rate of ASA was more significant if tablets were prepared with Eudragit L-100-55 as retarding substance rather than Eudragit S-100.

The dissolution rate of ASA was the highest from matrix tablets prepared with Lubritab as lubricant. Among other investigated samples with different lubricants, the differences in release rate of ASA were found to be minimal, regardless of the water solubility of lubricants.

The results obtained indicated that the suitability of the kinetic model was dependent on the type of Eudragit used. The release pattern for samples type S corresponded best to the Hixson–Crowell equation. For formulations type L the best-fitted kinetic model was the zero-order equation. It appears that in matrix formulations of ASA, the addition of fillers and lubricants to Eudragit L-100-55 as retarding substance gives a practical way to obtain a release rate approaching zero-order. Further investigations will gain additional information.

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