

Formulation and Evaluation of Salbutamol Sulphate Tablets Prepared by Direct Compression Using Various Excipients: Statistical Comparison of Dissolution Methods and Tablet Properties

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Formulation and Evaluation of Salbutamol Sulphate Tablets Prepared by Direct Compression Using Various Excipients: Statistical Comparison of Dissolution Methods and Tablet Properties

Summary : The tablet formulation of salbutamol sulphate (SBS), which is an antiasthmatic drug, was studied. It was aimed to investigate the effect of some excipients such as insoluble fillers and different disintegrants on the physical properties of salbutamol sulphate tablet formulations in this study. Meanwhile, the physical parameters and in vitro dissolution rates of SBS tablet available on the Turkish drug market were also investigated. Apparatus I and II (USP XXIV) in the dissolution test and UV spectrophotometric method were used for the assay of the active substance.

Paddle and basket dissolution test results were evaluated with DUNCAN test and a significant difference was found when compared statistically.

Keywords: Salbutamol sulphate tablets, Duncan test, Turkish drug market, In vitro availability, Rotating basket method, Paddle method, Kinetic evaluation.

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Çeşitli Yardımcı Maddeler Kullanılarak Direkt Basım Yöntemi ile Hazırlanan Salbutamol Sülfat Tabletlerinin Formülasyonu ve Değerlendirilmesi: Dissolüsyon Yöntemlerinin ve Tablet Özelliklerinin İstatistiksel Karşılaştırılması

Özet: Antiastmatik etkili bir madde olan salbutamol sülfatın (SBS) tablet formülasyonu üzerinde çalışıldı. Bu çalışmada salbutamol sülfat tablet formülasyonlarının fiziksel özellikleri üzerine farklı dağıtıcı maddelerin ve çözünmeyen dolgu maddelerinin etkisinin incelenmesi amaçlandı. Ayrıca, Türk ilaç piyasasındaki salbutamol sülfat tabletlerinin fiziksel parametreleri ve in vitro çözünme hızları da araştırılmıştır. Etken maddenin tayini için UV spektrofotometrik yöntem ve çözünme deneyleri için palet ve sepet (USP XXIV) yöntemleri kullanılmıştır.

Palet ve sepet çözünme testi sonuçları DUNCAN testi kullanılarak değerlendirildi ve istatistiksel olarak karşılaştırıldığında farkın önemli olduğu bulundu.

Anahtar kelimeler: Salbutamol sülfat tabletleri, Duncan testi, Türk ilaç piyasası, İn vitro uygunluk, Dönen sepet yöntemi, Palet yöntemi, Kinetik değerlendirme.

Introduction

Salbutamol sulphate (SBS) is a sympathomimetic amine which is used as a bronchodilator in the treatment of reversible bronchospasm. Its usual dose is 2-4 mg, 3-4 times a day¹. It is generally administered as tablet, capsule, syrup and spray. Only three different brands of salbutamol sulphate tablets are being marketed in Turkey².

Salbutamol is well absorbed following oral administration with peak plasma levels occurring within 1 to 4 hours (t_{max}). Despite the fact that salbutamol is

well absorbed, its systemic bioavailability is only 50% due to extensive presystemic metabolism in the intestinal wall. The pharmacokinetics of SBS and its sulphate conjugate metabolite have been investigated after IV and oral administration of SBS^{3,4}. Salbutamol is almost exclusively metabolised by conjugation to a 4'-o-sulphate ester in the intestinal wall and liver. A second minor metabolite has been reported³⁻⁵. Side effects of salbutamol were reported to be minimal and well tolerated. However some side effects such as tachycardia, palpitation, tremor, muscle cramps, peripheral vasodilation, nervousness and metabolic effects have been observed^{5,6}.

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Tablets prepared by direct compression are very popular dosage form among solid medicinal preparations because of high production rates and fewer processing procedures. The compression properties of most drugs are extremely poor and necessitates the inclusion of compression aids. The success of such a product design and development is mainly determined by the selection of suitable excipients⁷. Excipients have traditionally been classified according to the function they perform in a formulation, although many excipients perform multiple functions. Diluents allow the formulation of a practically sized tablet and can form a large proportion by weight of a formulated product when, for example, the active ingredient is very potent⁸. When the drug dose is less than 50 mg, tablets can usually be prepared by direct compression, but at higher doses the preferred method would be wet massing. SBS is very potent and soluble in water. Its usual dose is 2-4 mg; 3-4 times a day⁶. So, SBS was chosen as a model drug in the present study.

Effect of soluble and insoluble fillers on tablet properties were investigated by different research groups⁸⁻¹⁰. Jackson et al.⁸ investigated the effect of diluents on triamterene tablet which is a hydrophobic drug. It was shown to dissolve more rapidly when it was formulated with hydrophilic fillers such as lactose and starch as compared with insoluble diluents.

Due to its excellent compactibility, microcrystalline cellulose (MCC) is one of the most preferred filler-binders in direct compression tablet formulations¹¹. Another calcium salt for direct compaction is a specially processed grade of calcium sulphate dihydrate. Dicalcium phosphate dihydrate (Emcompress) is used for direct compaction of tablets, and has better compactibility than calcium sulphate dihydrate¹². Avicel has indeed better compactibility properties than Emcompress. Disintegrants tend to swell when wetted and so are added to a formulation to facilitate the break down of the dosage form into granules and powder particles. The newer disintegrants, called superdisintegrants, cause an extremely rapid break up of a tablet owing to their ability to swell to many times their original size^{8, 13, 14}. In this study we used sodium starch glycolate as a superdisintegrant.

Lubricants tend to be hydrophobic substances that act by coating particles to prevent adhesion of the tablet to the dies and punches of the tableting machine, to aid in ejection of the tablet from the die by reducing the interparticulate friction and improving flow of the powder mixture¹⁰. Glidants improve the flow properties of powders. Aerosil and talc were used as a glidant and a lubricant in this direct compression technique.

The first objective of the present study was to investigate the effect of insoluble fillers and other excipients on the physico-pharmaceutical properties and release profiles of SBS tablet formulations prepared in our laboratory. The possible quality and quantity differences were compared with commercial brands.

The second objective of this study was to examine the pharmaceutical properties and the differences of in vitro dissolution rates among the commercial tablets containing salbutamol sulphate. The quality of a product directly or indirectly affects the safety, effectiveness and acceptability of the product. Therefore its pharmaceutical properties should meet the official requirements and specifications of the finished product^{10, 11}.

In this study, six tablet formulations of SBS were developed and the effect of various excipients on quality controls of the tablets was investigated, by using Apparatus I and II according to USP XXIV¹⁵. Controls on disintegration and dissolution rate, friability, hardness, weight deviation and diameter, thickness and their properties on T.F. 1974¹⁶ and other pharmaceutical standards of six different SBS tablets formulations prepared in our laboratory and produced by various companies in Turkey were accomplished.

Material and Methods

Materials

Salbutamol sulphate (Glaxo Pharm. Comp. Turkey); microcrystalline cellulose (Avicel® pH 101, Marcus

Hook Pennsylvania, USA); dibasic calcium phosphate dihydrate (Emcompress[®], Riedel-de Haën AG/Seelzcanover); soluble starch (E. Merck, Germany), talc, calcium carbonate, calcium sulphate 2H₂O (E. Merck, Germany); sodium starch glycolate (Primogel, Mendell USA); colloidal silicium dioxide (Aerosil R200, Degussa Inc. USA); corn starch (Piya-le, Turkey) and other chemicals were of pharmaceutical grade. Commercial SBS tablets available in Turkish pharmaceutical market were tested in this study. 2.4 mg of SBS is equivalent to 2 mg of salbutamol, and 4.8 mg of SBS is 4 mg of salbutamol in the commercial conventional tablets^{2, 15, 17}.

Methods

Preparation of salbutamol sulphate tablets

SBS, insoluble fillers and disintegrant were mixed by geometric dilution in a jar for one hour. Then the mixture of talc-aerosil was added and mixed for ten minutes. Tablets were compressed by hand using a single-punch tableting machine.

The various excipients and their amounts which are used in formulations were given in Table 1. The commercial SBS tablets investigated in this study were shown in Table 2.

Table 1. The codes and formulations of SBS tablets prepared in the study.

Ingredients (mg)	Codes					
	T1	T2	T3	T4	T5	T6
SBS	4	4	4	4	4	4
Avicel PH 101	85	85	85	85	85	85
Emcompress	105	85	-	-	-	-
Soluble starch	-	20	-	-	-	-
Calcium carbonate	-	-	105	85	-	-
Corn starch	-	-	-	20	-	-
Calcium sulphate	-	-	-	-	105	85
Primogel	-	-	-	-	-	20
Talc	4	4	4	4	4	4
Aerosil	2	2	2	2	2	2
Total weight (mg)	200	200	200	200	200	200

Table 2. The codes of commercial SBS tablets tested in the study.

Codes	Label dose (mg/tablet)	Serial number
S2	2.4	712017
V2	2.4	004
V4	4.8	005

In this study, different types of excipients were studied: Microcrystalline cellulose, dicalcium phosphate dihydrate, calcium carbonate, calcium sulphate dihydrate, corn starch, soluble starch and sodium starch glycoate. Aerosil and talc were used as glidant and lubricant. Due to its excellent compactibility, microcrystalline cellulose (MCC) is one of the most preferred filler-binders in direct compression tablet formulations⁷.

The physical properties of tablets

The formulated and commercial tablets were evaluated for uniformity of weight¹⁶ and thickness (micrometer, USSR), hardness (Monsanto, Hardness tester), friability (Aymes friabilator) and disintegration time (Disintegration apparatus, D 69 Z Aymes)¹⁵. The controls applied on all of the tablets were the following:

Weight variation: Weight variation studies of twenty tablets for each batch were carried out according to the method indicated T.F. 1974¹⁶. Twenty tablets were weight first individually and all together for this purpose and resulting deviation were determined.

Hardness: Ten tablets from each batch were examined using Monsanto hardness tester.

Disintegration time: The tablets were examined using the USP XXIV disintegration apparatus¹⁵. Five tablets were tested for each batch. The disintegration time of tablets was compared to 15 minutes which is accepted as the general tablet disintegration time by T.F. 1974¹⁶.

Diameter-thickness ratio: It's accomplished on ten tablets by measuring diameter thickness values.

Friability: For friability tests, ten tablets were weighed (W_1) and rotated at one hundred revolutions for 4 min. in a Roche friabilator. The tablets were then reweighed (W_2) and the percentage of friability (%F) was calculated.

Content uniformity: Spectrophotometric method was used to check the content uniformity of the tablets. For this purpose; after the crushing of the twenty tablets, distilled water was added and the volume was adjusted to 10 ml. The mixture was shaken for 30 minutes by automatic shaker, and then SBS contents of the tablets were determined spectrophotometrically at 277 nm (UV-spectrophotometer, Shimadzu UV-1208)¹⁸. Content uniformity studies were examined in triplicates for twenty tablets of each batch. Regression equation and regression coefficients were calculated to be $y=167x + 0.742$ (y =concentration ($\mu\text{g}/\text{ml}$), x =absorbance) and $r=0.998$, respectively.

Dissolution rate determination: The tablets were examined using Apparatus I and II of USP XXIV (Dissolution apparatus, PTW 2 Pharma test) at 100 rpm and 50 rpm, respectively. The dissolution medium was 500 ml distilled water at a temperature of $37\pm 0.5\text{ }^\circ\text{C}$ ¹⁵. Six samples from each batch were assayed spectrophotometrically at 277 nm and the means were calculated for plotting.

Kinetic studies: The kinetic analysis of the dissolution data was evaluated by a computer programme for zero, first order, Hixson-Crowell, Modified Hixson Crowell, RRSBW kinetics¹⁹.

Statistical methods: Statistical evaluation of dissolution rates of formulated and commercial tablets was performed using Duncan/One Way Anova test, and $p<0.05$ was considered to be statistically significant. Otherwise, the statistical evaluation of two dissolution methods of tablets (basket and paddle) was performed using Anova test. Differences between treatments were tested using DUNCAN multiple comparison, and $p<0.05$ was considered to be statistically significant²⁰.

Results and Discussion

The results obtained from the quality control tests were given in Table 3. Some information exists about salbutamol sulphate and its dosage forms in USP-NF 2000 and in BP 1998. For this reason the test results obtained were compared with the specifications of finished product and general requirements^{15, 18}.

Table 3. The physical parameters of salbutamol sulphate tablets.

Tablet code	Weight (mg) $\bar{x}\pm\text{CL}$	Amount of active agent (mg)	Diameter*/thickness Ratio (mm) $\bar{x}\pm\text{CL}$	Hardness (kg) $\bar{x}\pm\text{CL}$	Friability (%)	Disintegration time (sec.) $\bar{x}\pm\text{CL}$
T1	200.9 \pm 1.2	4.08	4.5 \pm 0.3	2.0 \pm 0.3	2.44	3.0 \pm 0.9
T2	200.6 \pm 1.4	4.07	4.2 \pm 0.1	3.2 \pm 0.3	0.64	5.4 \pm 0.7
T3	198.9 \pm 1.5	4.01	4.4 \pm 0.3	1.5 \pm 0.3	2.85	15.2 \pm 1.0
T4	198.7 \pm 1.0	4.09	4.3 \pm 0.1	2.7 \pm 0.2	0.91	6.0 \pm 0.9
T5	201.0 \pm 0.9	4.06	4.3 \pm 0.1	2.5 \pm 0.3	1.00	11.4 \pm 1.4
T6	201.4 \pm 1.1	4.10	4.1 \pm 0.1	2.5 \pm 0.3	1.24	4.0 \pm 0.4
S2	126.8 \pm 0.6	2.35	2.1 \pm 0.1	1.9 \pm 0.1	0.91	80.2 \pm 7.1
V2	121.0 \pm 1.4	2.38	2.5 \pm 0.1	2.1 \pm 0.1	0.47	39.0 \pm 5.7
V4	200.8 \pm 1.6	4.78	3.1 \pm 0.2	1.1 \pm 0.2	0.72	39.2 \pm 4.9

* Diameter of formulated tablets is 9.2 mm.; diameter of commercial tablets are 6.6, 6.7 and 8.7 mm for S2, V2 and V4 coded tablets consequently.

All tablets were found to satisfy the USP and BP requirements for weight uniformity. In this study, it was determined that the weights of the tablets prepared in our laboratory were changing between 198.7 \pm 1.0 – 201.4 \pm 1.1 ($\pm\text{CL}$) mg, it was found to be between 121.0 \pm 1.4 – 200.8 \pm 1.6 ($\pm\text{CL}$) mg in commercial SBS tablets. The commercial and the formulated tablets' weight variations were not over the pharmacopoeia limits^{15, 18}.

In our study, the diameter/thickness ratios of the tablets determined are shown in Table 3. In pharmacopoeias there is no records about the diameter/thickness ratio of the tablets. But Rudnic et al.²¹, mentioned that $\pm 5\%$ difference in thickness could be accepted. However, there were no differences in all the tablets. Diameter/thickness ratio must be four according to Güven²². This ratio was changing between 4.1 \pm 0.1 - 4.5 \pm 0.3 ($\pm\text{CL}$) in formulated SBS tablets and 2.1 \pm 0.1 - 3.1 \pm 0.2 ($\pm\text{CL}$) in commercial tab-

lets. In the literature, it was seen that there were tablets which did not have diameter/thickness ratio as four but nothing clear about what could be the harmful²³.

According to the B.P. 1998 the amount of salbutamol in the tablets has to be between 92.5-107.5%. It seems that the amount of drug substance in the all tablets was in the required limits. Table 3 presents the amount of SBS in the tablets.

The recommended value for tablet hardness is 4-8 kg^{24, 25}. In our experiments the average hardness of the tablets was found in values between 1.5±0.3 - 3.2±0.3 (±CL) kg in formulated SBS tablets; 1.1±0.2 - 2.1±0.1 (±CL) kg in commercial SBS tablets. Generally the disintegration times are related to hardness. In the literature, it was cited that, when the hardness increase, the disintegration time increases and the dissolution rate also delays^{24, 26, 27}. However, contrary results were observed with T2 coded tablets. Although the tablets have the highest hardness value among others, they gave the shorter disintegration time as 5.4 sec. T1 and T6 coded tablets gave the shortest disintegration times as 3 and 4 seconds, respectively. The tablet coded T2 followed T6 when their disintegration times were compared. Besides this, the disintegration time was found to be 15.2±1.0 (±CL) sec in the T3 coded tablet which contains calcium carbonate as insoluble filler. So, these results indicate that, Primogel, which shows the disintegration action by way of swelling, and corn starch increases the liquid penetration into the tablets. Avicel also improves the disintegrating action through the capillarity action of water penetration^{7, 28}. In this study, the disintegration times of all tablets were less than 15 minutes as given in T.F. 197411. The disintegration times changed between 3.0±0.9 - 15.2±1.0 (±CL) seconds in formulated SBS tablets; and 39.0±5.7 - 80.2±7.1 (±CL) seconds in commercial tablets. According to the pharmacopoeia the disintegration values were quite suitable for the formulated and the commercial SBS tablets¹⁶.

The results of the friability studies are shown in Table 3. Shafer et al.²⁹, mentioned that a loss was not

more than 1% was normal but especially less than 0.8% of loss was also considered as normal. The friability values of tablets investigated were generally low except for T1 and T3. As seen Table 3, T1 and T3 coded tablets which contained Avicel/Emcompress and Avicel/Calcium carbonate, exhibited high friability values. As explained in a previous study, a general problem of tablets compressed from different calcium phosphates is their high friability¹². The variation between the hardnesses of the formulations is assumed to be consequence of different compression pressures.

It was reported that effect of the lubricant on crushing strength depends on the active substance and excipients in the tablet formulation³⁰. Talc is not an anti-friction lubricant and presents a high elastic behaviour. It is poorly flowing powder. Nevertheless, Aerosil was added for improving the flow in this study. It was shown that type of excipients could be the reason of the high friability in many reports. As reported in previous studies, it can be said that the amount and type of the excipients are the reason of the high friability³¹⁻³³. Our findings agree with these reports. In general, increase in tablet hardness causes lower friability values and longer disintegration times. But considering the results of all the brands and formulated tablets together no such correlation could be observed in this study.

The fastest dissolution was obtained from the formulation T6 as it could be seen from Figures 1, 2. It is possible to say that, this result was caused by the Primogel, a disintegrant used in formulation T6. This finding agree with the earlier reports^{8, 28, 34}. T1 and T2 formulations include an insoluble filler Em-

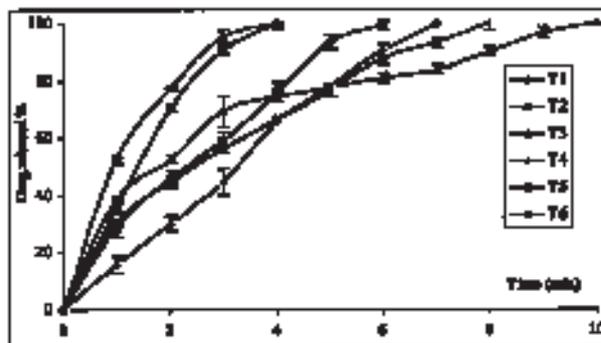


Fig. 1. The dissolution profiles of SBS tablets obtained by USP XXIV basket method.

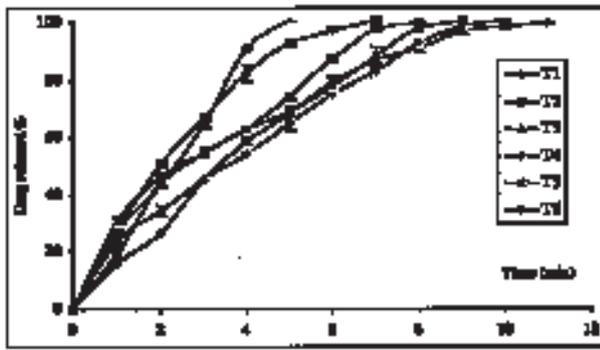


Fig. 2. The dissolution profiles of SBS tablets obtained by USP XXIV paddle method.

compress. T2 formulation included soluble starch in addition but it didn't cause any advantage. No faster dissolution was observed from T2. In formulation prepared with direct compression method, the release of the drug was fast and the dissolved amount of the drug reached 100%. This fast release phenomenon was reported in the studies involving Avicel in which direct compression method was used^{35, 36}. A similar situation was seen in T5 and T6 formulations. Primogel in T6 shortened the dissolution and disintegration time. In both of T3 and T4

formulations, Avicel and insoluble filler calcium carbonate were used. In T4 formulation, corn starch was included in addition. The disintegration and dissolution times were found significantly shorter than T3.

On the other hand, it was thought that using basket method for an immediate disintegrating dosage form was not suitable. Evaluating statistically, it was shown that similar results were reported in some previous studies^{23, 37, 38}. It might be shown that the differences between the formulations according to the dissolution methods were significant.

There is no record about the dissolution time in USP XXIV SBS monographs. In basket method, T1 and T2 formulations released the drug substance in 99.9%, 4 min and 99.4%, 6 min, respectively. However in paddle method these values were observed in 100.3%, 7 min and 99.6%, 8 min, respectively. The tablet coded T6 with the most fast release, gave 101% with paddle and 100% with basket method (Table 4, 5). It was shown by many investigators that

Table 4. Dissolution data using Duncan test.

	Tablet code	Mean	Standard deviation	Standard error	95% Confidence interval for mean	
					Lower boundary	Upper boundary
Basket method	T1	99.913	0.423	0.244	98.861	100.965
	T2	99.368	1.785	1.030	94.934	103.803
	T3	99.955	0.050	0.028	99.462	100.449
	T4	99.836	0.231	0.133	99.262	100.410
	T5	100.515	2.952	1.704	93.182	107.849
	T6	100.026	1.820	1.050	95.505	104.547
	S2	99.660	0.923	0.533	97.366	101.953
	V2	99.551	1.318	0.761	96.275	102.826
Paddle method	V4	99.106	0.837	0.483	97.025	101.187
	T1	100.284	0.852	0.492	98.167	102.401
	T2	99.600	0.117	0.068	99.307	99.892
	T3	98.146	0.735	0.424	96.319	99.974
	T4	100.276	0.060	0.034	100.125	100.425
	T5	100.106	0.102	0.059	99.851	100.361
	T6	100.671	0.564	0.325	99.269	102.072
	S2	99.955	0.050	0.029	99.829	100.082
	V2	99.366	0.315	0.182	98.582	100.150
	V4	99.880	1.080	0.624	97.194	102.565

Table 5. The results of the Post Hoc Tests using Duncan Test.

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	7928.344 ^a	17	466.373	118.358	.000
Intercept	45854.121	1	45854.121	11637.042	.000
Formulation	2922.500	8	365.312	92.710	.000
Method	3166.695	1	3166.695	803.657	.000
Formulation* Method	1839.149	8	229.894	58.343	.000
Error	141.853	36	3.940		
Total	53924.318	54			
Corrected Total	8070.197	53			

^aR² = 0.982)

at low route levels (50 rpm) the selectivity characteristics of the dissolution method were more definite^{23, 24}. According to the results presented in figures 1-3, the amount of SBS dissolved with paddle method is greater than that of the basket method. This

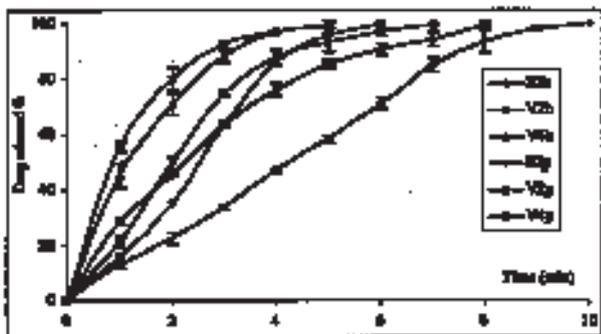


Fig. 3. The dissolution profiles of commercial SBS tablets obtained by USP XXIV basket and paddle method.

greater amount of dissolved drug may be directly related to the agitation rate of the paddle. A remarkable difference between the two methods was not found because of the solubility characteristics of drug (SBS). However, the difference was important between six formulations containing various excipients and three commercial tablets, according to Duncan test results ($p < 0.05$; CI 95%). There are various quality control studies comparing the effect of two different dissolution method. In a previous study, the dissolution rate of indomethacin was faster with paddle method rather than that of the basket method³⁷. This report agree with our study. Paddle and basket dissolution test results were evaluated with DUNCAN test and a significant difference was noticed when compared statistically ($p < 0.05$). The differences between the methods and formulations were found to be significant statistically. All statistical results are listed in Table 4, 5.

The best harmony was obtained for Modified Hixson Crowell kinetic model and RRSBW kinetics in the written order (Table 6, 7). The evaluation of the kinetic results indicated that formulated and commercial SBS tablets for rotating basket and paddle dissolution methods seem to comply with Modified Hixson-Crowell kinetic model according to the determination coefficient (r^2), sum of squared deviations (SSD), sum of weighted squared deviations (SWSD) and Akaike's Information Criteria (AIC) values (Table 6, 7). Figures 4-6 also supported this fin-

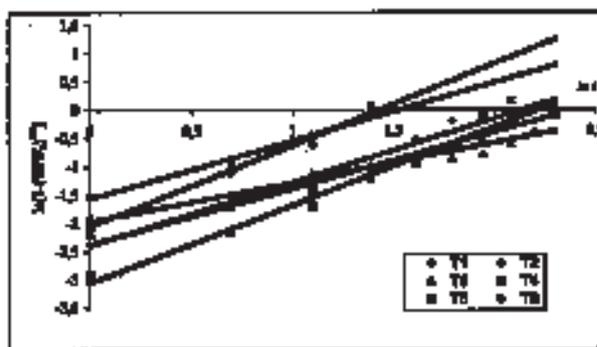


Fig. 4. The plot of kinetic model, Modified Hixson Crowell for SBS tablets according to the basket method.

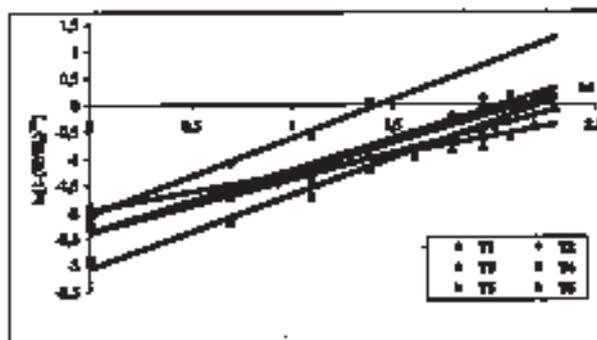


Fig. 5. The plot of kinetic model, Modified Hixson Crowell for SBS tablets according to the paddle method.

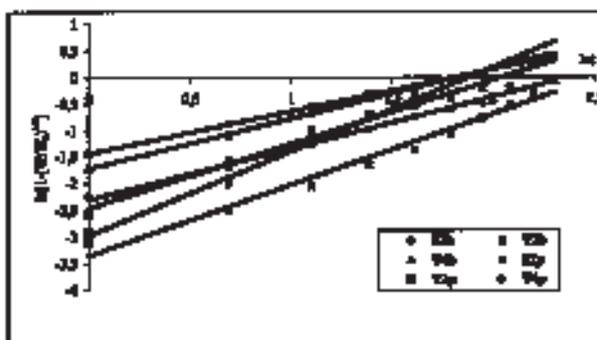


Fig. 6. The plot of kinetic model, Modified Hixson Crowell for commercial SBS tablets according to the basket and paddle method.

ding. Linear profiles were obtained by plotting $\ln[1 - (w/w_0)^{1/3}]$ versus $\ln t$ graph. The determination coefficients obtained from the linear regression analysis of the dissolution data were higher than 0.98.

Preparations are, in general, required to mimic in vivo conditions during the selection of an appropriate method for determination of dissolution rate^{38, 39}. Dissolution rate studies carried out with low routes provide more reliable results about the bioavailability^{23, 38}.

Table 6. The kinetic assessment of release data for basket method.

Kinetic model Code	Modified Hixson-Crowell		First order		Zero order		Hixson-Crowell		RRSW	
	a	b	Kr	r ²	Kr ⁰	r ²	K	r ²	T _{max}	β
T1	0.1906	0.184	56.61	0.982	9.399	0.907	7.178	0.978	1.32	1.342
	0.873x10 ⁻²	0.989	0.144x10 ⁻¹	0.989	0.130	0.907	0.266x10 ⁻²	0.978	0.983	0.983
	0.398x10 ⁻¹	0.989	0.636x10 ⁻¹	0.989	0.207	0.907	0.17x10 ⁻¹	0.978	0.205x10 ⁻¹	0.983
	-34.17	0.989	-14.95	0.989	-3.58	0.907	-21.71	0.978	0.12x10 ⁻¹	0.983
									-30.75	
T2	1.303	0.124	42.37	0.960	17.07	0.940	5.523	0.994	2.43	1.377
	0.177x10 ⁻²	0.983	0.163	0.983	0.829x10 ⁻¹	0.940	0.782x10 ⁻²	0.994	0.983	0.983
	0.766x10 ⁻¹	0.983	0.849	0.983	0.524x10 ⁻¹	0.940	0.268x10 ⁻¹	0.994	0.513x10 ⁻²	0.983
	-33.98	0.983	-8.81	0.983	-18.93	0.940	-27.74	0.994	0.198x10 ⁻¹	0.983
									-27.62	
T3	0.650	0.050	19.75	0.897	3.574	0.909	2.783	0.957	2.73	0.836
	0.871x10 ⁻²	0.967	0.265x10 ⁻¹	0.967	0.528	0.909	0.937x10 ⁻¹	0.957	0.937	0.937
	0.686x10 ⁻¹	0.967	0.132	0.967	0.777	0.909	0.195	0.957	0.119x10 ⁻¹	0.937
	-43.42	0.967	-34.28	0.967	-2.368	0.909	-21.56	0.957	0.963x10 ⁻¹	0.937
									-40.28	
T4	1.344	0.102	34.44	0.874	17.27	0.987	4.182	0.964	3.61	1.585
	0.496x10 ⁻²	0.988	0.467	0.988	0.842x10 ⁻²	0.987	0.624x10 ⁻¹	0.964	0.966	0.966
	0.246x10 ⁻¹	0.988	2.328	0.988	0.672x10 ⁻²	0.987	0.166	0.964	0.128x10 ⁻¹	0.966
	-35.13	0.988	-3.319	0.988	-29.43	0.987	-17.41	0.964	0.533x10 ⁻¹	0.966
									-26.43	
T5	0.889	0.074	28.06	0.904	11.77	0.882	5.939	0.977	3.10	1.103
	0.818x10 ⁻²	0.974	0.132	0.974	0.133	0.882	0.381x10 ⁻¹	0.977	0.942	0.942
	0.446x10 ⁻¹	0.974	0.780	0.974	0.148	0.882	0.336x10 ⁻¹	0.977	0.168x10 ⁻¹	0.942
	-34.44	0.974	-14.18	0.974	-12.11	0.882	-34.72	0.977	0.789x10 ⁻¹	0.942
									-28.68	
T6	1.229	0.197	69.25	0.974	25.08	0.922	8.28	0.989	1.73	1.578
	0.299x10 ⁻³	0.998	0.157	0.998	0.539x10 ⁻¹	0.922	0.963x10 ⁻¹	0.989	0.998	0.998
	0.233x10 ⁻²	0.998	0.920	0.998	0.216x10 ⁻¹	0.922	0.300x10 ⁻¹	0.989	0.322x10 ⁻³	0.998
	-28.43	0.998	-5.40	0.998	-7.68	0.922	-16.96	0.989	0.192x10 ⁻²	0.998
									-28.16	
S2	0.941	0.087	24.85	0.964	3.892	0.917	3.360	0.996	2.83	1.173
	0.941x10 ⁻²	0.997	0.285x10 ⁻¹	0.997	0.192	0.917	0.202x10 ⁻²	0.996	0.988	0.988
	0.438x10 ⁻¹	0.997	0.861x10 ⁻¹	0.997	0.240	0.917	0.741x10 ⁻²	0.996	0.283x10 ⁻²	0.988
	-31.74	0.997	-27.05	0.997	-8.17	0.917	-47.63	0.996	0.128x10 ⁻¹	0.988
									-42.99	
V2	0.778	0.136	54.73	0.988	6.430	0.948	6.670	0.975	1.26	1.119
	0.169x10 ⁻¹	0.994	0.497x10 ⁻¹	0.994	0.305	0.948	0.180x10 ⁻¹	0.975	0.995	0.995
	0.775x10 ⁻²	0.994	0.254x10 ⁻¹	0.994	0.445	0.948	0.776x10 ⁻¹	0.975	0.760x10 ⁻⁶	0.995
	-39.40	0.994	-24.31	0.994	-1.93	0.948	-18.07	0.975	0.534x10 ⁻²	0.995
									-31.90	
V4	0.909	0.132	46.83	0.975	7.979	0.883	5.912	0.970	1.98	1.223
	0.673x10 ⁻³	0.990	0.173x10 ⁻¹	0.990	0.190	0.883	0.316x10 ⁻³	0.970	0.987	0.987
	0.170x10 ⁻²	0.990	0.677x10 ⁻¹	0.990	0.247	0.883	0.301x10 ⁻¹	0.970	0.178x10 ⁻²	0.987
	-32.31	0.990	-18.25	0.990	-4.30	0.883	-26.77	0.970	0.111x10 ⁻¹	0.987
									-27.62	

K, Kr, Kr⁰: Release rate constants^{38,41} (mg/hour/cm²; hour⁻¹; mg/hour)
 r²: Determination coefficient
 β: The shape factor^{41,43}
 T_{max}: Time (min.)
 SSD: Sum of squared deviations
 SWSD: Sum of weighted squared deviations
 AIC: Akaike's information criteria

Table 7. The kinetic assessment of release data for paddle method.

Kinetic model Code	Modified Higgin-Crowell		First order		Zero order		Higgin-Crowell		KRSBW	
	a	b	Kr	r ²	Kr ⁰	r ²	K	r ²	T _{0.5%}	β
T1	1.057	0.112	38.28	0.976	7.133	0.913	4.040	0.989	2.94	1.335
	0.996	0.872x10 ⁻¹	SSD	0.138	SSD	0.144	SSD	0.254x10 ⁻²	r ²	0.990
	0.130x10 ⁻¹	0.683	SWSD	0.683	SWSD	0.129	SWSD	0.142x10 ⁻¹	SSD	0.397x10 ⁻²
	-43.31	-11.83	AIC	-11.83	AIC	-9.56	AIC	-39.81	SWSD	0.168x10 ⁻¹
									AIC	-34.88
T2	1.107	0.089	24.03	0.990	6.642	0.963	3.184	0.958	3.38	1.351
	0.979	0.121x10 ⁻¹	SSD	0.113	SSD	0.747x10 ⁻¹	SSD	0.223x10 ⁻¹	r ²	0.955
	0.621x10 ⁻¹	0.493	SWSD	0.493	SWSD	0.360x10 ⁻¹	SWSD	0.107	SSD	0.215x10 ⁻¹
	-31.27	-13.39	AIC	-13.39	AIC	-16.74	AIC	-28.19	SWSD	0.113
									AIC	-34.54
T3	0.984	0.067	23.78	0.938	4.750	0.943	2.891	0.992	3.86	1.233
	0.984	0.744x10 ⁻¹	SSD	0.178	SSD	0.186	SSD	0.994x10 ⁻²	r ²	0.959
	0.314x10 ⁻¹	0.170	SWSD	0.170	SWSD	0.132	SWSD	0.319x10 ⁻¹	SSD	0.205x10 ⁻¹
	-49.80	-12.03	AIC	-12.03	AIC	-14.48	AIC	-48.72	SWSD	0.840x10 ⁻¹
									AIC	-38.73
T4	1.191	0.075	28.41	0.879	5.796	0.971	2.631	0.989	4.36	1.442
	0.988	0.638x10 ⁻¹	SSD	0.588	SSD	0.578x10 ⁻¹	SSD	0.446x10 ⁻¹	r ²	0.961
	0.440x10 ⁻¹	3.628	SWSD	3.628	SWSD	0.371x10 ⁻¹	SWSD	0.157	SSD	0.193x10 ⁻¹
	-46.33	-4.76	AIC	-4.76	AIC	-24.49	AIC	-29.09	SWSD	0.108
									AIC	-35.42
T5	0.831	0.062	21.82	0.862	3.039	0.983	2.825	0.941	3.33	1.044
	0.946	0.684x10 ⁻¹	SSD	0.684x10 ⁻¹	SSD	0.178	SSD	0.279x10 ⁻¹	r ²	0.902
	0.196x10 ⁻¹	0.380	SWSD	0.380	SWSD	0.228	SWSD	0.309	SSD	0.326x10 ⁻¹
	0.118	-22.13	AIC	-22.13	AIC	-11.50	AIC	-30.18	SWSD	0.176
	-31.35								AIC	-28.79
T6	1.254	0.141	36.29	0.897	11.33	0.981	4.786	0.996	2.44	1.333
	0.960	0.129x10 ⁻¹	SSD	0.147	SSD	0.138x10 ⁻¹	SSD	0.484x10 ⁻¹	r ²	0.982
	0.309x10 ⁻¹	0.566	SWSD	0.566	SWSD	-0.366x10 ⁻¹	SWSD	0.189	SSD	0.227x10 ⁻¹
	-17.73	-7.56	AIC	-7.56	AIC	-17.41	AIC	-13.14	SWSD	0.931x10 ⁻¹
									AIC	-14.91
S2	1.333	0.078	29.39	0.888	6.334	0.976	2.603	0.966	4.39	1.593
	0.983	0.117x10 ⁻¹	SSD	0.772	SSD	0.257x10 ⁻¹	SSD	0.113	r ²	0.956
	0.565x10 ⁻¹	0.332	SWSD	0.332	SWSD	-0.501x10 ⁻¹	SWSD	0.330	SSD	0.502x10 ⁻¹
	-40.40	-0.58	AIC	-0.58	AIC	-32.58	AIC	-19.58	SWSD	0.121
									AIC	-30.97
V2	1.170	0.123	37.18	0.998	7.307	0.834	4.124	0.974	2.58	1.430
	0.976	0.917x10 ⁻²	SSD	0.119	SSD	0.185	SSD	0.128x10 ⁻¹	r ²	0.994
	0.113	0.381	SWSD	0.381	SWSD	0.219	SWSD	0.419x10 ⁻¹	SSD	0.218x10 ⁻²
	-28.83	-12.85	AIC	-12.85	AIC	-7.77	AIC	-28.49	SWSD	0.121x10 ⁻¹
									AIC	-38.87
V4	1.333	0.144	46.99	0.966	10.39	0.935	4.330	0.987	2.86	1.539
	0.993	0.346x10 ⁻²	SSD	0.434	SSD	0.394x10 ⁻¹	SSD	0.734x10 ⁻¹	r ²	0.991
	0.337x10 ⁻¹	2.333	SWSD	2.333	SWSD	-0.507x10 ⁻¹	SWSD	0.168	SSD	0.454x10 ⁻²
	-29.99	-2.99	AIC	-2.99	AIC	-15.39	AIC	-13.50	SWSD	0.126x10 ⁻¹
									AIC	-28.35

K, Kr, Kr⁰: Release rate constants^{41,42} (mg/hour/cm²; hour⁻¹; mg/hour)

r²: Determination coefficient

β: The shape factor^{41,49}

T_{0.5%}: Time (min.)

SSD: Sum of squared deviations

SWSD: Sum of weighted squared deviations

AIC: Akaike's information criteria

The results obtained from this investigation on the invitro release characteristics of formulated SBS tablets and commercial SBS tablets marketed in Turkey indicated that all the tablets tested met the criteria specified by physical parameters. However, according to the in vitro dissolution rate results there were significant differences between the nine tablets formulations tested.

In our study, difference between two dissolution methods, basket and paddle could be explained from the view point of solubility characteristics of salbutamol sulphate. There were significant differences between the dissolution rate levels, due to the type of excipients (Table 5) ($p < 0.05$; CI 95%). Determination of the official norms is needed to eliminate the dissolution rate differences, which may produce bioavailability problems.

It could be concluded that, the dissolution rates of the formulated and commercial SBS tablets were found to be faster in the paddle method compared to the basket method ($p < 0.05$; CI 95%). Although the difference is statistically significant, the confidence intervals (CIs) indicate that the degree of confidence is low for these means.

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