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ÇÖZÜCÜYLE ADSORBLANMIŞ ASETAZOLAMİD SİSTEMLERİ İÇEREN KAPSÜL FORMÜLASYONLARI

CAPSULE FORMULATIONS CONTAINING SOLVENT DEPOSITED ACETAZOLAMIDE SYSTEMS

Betül DORTUNÇ * – Şükran ÇOLAK*

SUMMARY

Acetazolamide capsules were formulated using solvent deposited systems of the drug and the solid dosage form excipients Acdisol and Fast-Flo Lactose; 0.5% magnesium stearate was added as lubricant. The capsules were examined for content uniformity, disintegration time and dissolution rate. The data were compared to those of a commercially available acetazolamide tablet produced in Turkey.

ÖZET

Katı dozaj şekilleri yardımcı maddelerinden Acdisol ve Fast-Flo Laktoz kullanılarak, çözücüyle adborblanmış asetazolamid sistemlerinin kapsülleri hazırlanmıştır. Kaydırıcı olarak %0.5 magnezyum stearat ilave edilmiştir. Kapsüllerde içerik düzgünlüğü, dağılma süresi ve çözünme hızı tayinleri yapılmış, elde edilen sonuçlar Türkiye piyasasında bulunan bir tablet preparatı ile karşılaştırılmıştır.

INTRODUCTION

Acetazolamide is a carbonic anhydrase inhibitor and is widely used as a diuretic drug or in the treatment of glaucoma (1). As this drug is poorly water soluble, its bioavailability may be dissolution rate limited, as shown by some authors (2). For this reason a dissolution test for acetazolamide tablets is specified in the USP (3).

In our previous study solvent deposited acetazolamide systems were prepared to achieve more rapid and reproducible rates of dissolu-

* MarmaraÜniversitesi Eczacılık Fakültesi, Farmasötik Teknoloji Anabilim Dalı, Nişantaşı/ISTANBUL.

tion (4). Among the systems prepared and tested, those containing 5% Acdisol, 5% Avicel, 5% Fast-Flo Lactose, 25% Aerosil and 50% Primojel gave the best results.

The objective of this work was to formulate capsules with three of these systems and to evaluate them. The systems with 5% Acdisol, 5% Avicel and 5% Fast-Flo Lactose were chosen because of their high drug-to-carrier ratio being an advantage in formulating capsules of a proper size. A commercial acetazolamide tablet preparation locally manufactured was also tested and compared to the experimentally produced capsules.

EXPERIMENTAL

Materials

Acetazolamide (DIF-Turkey)
Acdisol (FMC Corp.-USA)
Avicel PH 102 (FMC Corp.-USA)
Fast-Flo Lactose (Foremost-McKesson, Inc.-USA)
Magnesium stearate (Pür Kimya-Turkey)
Commercial tablets containing 250 mg acetazolamide.
Other chemicals and solvents were of analytical grade and were used as received.

Apparatus

Tapped density volumeter (Aymes)
Sieving machine vibro (Retsch)
Disintegration tester (Dener Fizik, TD-1)
Dissolution tester (Aymes)
Spectrophotometer (Varian, Techtron Series 634)
Tablet hardness tester (Monsanto)
Friabilitor (Aymes)
Membrane filter (0.45 μm, Sartorius)

METHODS

Studies on the properties of the solvent deposited systems, ingredients and blends (5):

Bulk density

2 g of powder was carefully poured into a 10 ml cylinder and the volume was recorded. The results are the mean of three experiments.

Tapped density

The 2 g samples mentioned above were then tapped using a volumeter and the volumes after 50 taps were noted.

Compressibility

The compressibility was calculated as follows,

$$\text{Comp.\%} = \frac{\text{tapped density - bulk density}}{\text{tapped density}} \times 100$$

Angle of repose

A funnel was fixed with its tip at a given height. The outlet was closed and the funnel was filled with the sample, which was then allowed to pour out. The diameter of the conical pile so formed was measured and the angle of repose was calculated by the formula:

$$\text{tg } \alpha = \frac{h}{r}$$

Formulation and preparation of the capsules

The three formulations used in this study are given in Table I. The powders, except for the lubricant, were bag blended for 25 min, then

Table-I: Composition of the capsule formulations.

Substance	Composition (%)	Quantity per capsule (mg)
Solvent deposited acetazolamide system	82.50	105.00*
Fast-Flo Lactose	15.00	19.05
Acdisol	2.00	2.50
Mg-stearate	0.50	0.63
Total	100.00	127.18

* Amount equivalent to 100 mg pure drug.

magnesium stearate was added and mixed for 5 min. The excipients were sieved through a 125 μm sieve before using. Samples were then filled by hand into hard gelatin capsules of size one. Each capsule was individually weighed before filling.

Evaluation of the experimental capsules and the commercial tablets

Weight variation

Ten samples were examined.

Content uniformity

Acetazolamide content of ten samples were determined using the method of the Turkish Pharmacopeia 1974 (6).

Hardness

Ten tablets were examined using Monsanto hardness tester.

Friability

The test was carried out with twenty tablets and a Roche friabilitor was used with 100 rpm for 4 min.

Disintegration time

Six samples were examined using an apparatus of USP XXI standarts.

Dissolution rate

This test was carried out using the USP XXI procedure specified for acetazolamide tablets (3). At preset time intervals aliquots of 1 ml were withdrawn by means of a pipette adapted with a membrane filter and immediately replaced by the same volume of dissolution medium. Aliquots were diluted to 25 ml with acetate buffer and assayed spectrophotometrically at 265 nm. The amount dissolved was determined by using a calibration curve. At least 3 samples were used for each determination.

RESULTS AND DISCUSSION

A basic capsule formulation consisting of a diluent, a disintegrant and a lubricant was applied to three solvent deposited acetazolamide systems prepared with 5% Acdisol, 5% Avicel and 5% Fast-Flo Lactose and showing high drug release rates (4). As diluent Fast-Flo Lactose was chosen, it consists mainly of spherical aggregates of microcrystals and is highly fluid, furthermore formulations with Fast-Flo Lactose usually show good release rates (7). Acdisol is a relatively new disingteg-

rant, effective even in very low concentrations (8, 9). As lubricant magnesium stearate was used, as it is an efficient lubricant and probably the most widely used in capsule formulations.

As shown in Table II the flow properties of the systems, ingredients and blends were evaluated by means of compressibility and angle of repose measurements (5). The flow of the pure drug is fair, whereas the solvent deposited systems show good flow properties, when regarding the compessibility. There isn't always a correlation between compressibility and angle of repose, e.g. for the solvent deposited systems, the angle of repose values point out a fair to good flow. Compressibilitiy values of Acdisol and Fast-Flo Lactose are fair and excellent respectively. So the addition of these ingredients in the mentioned low ratios was supposed not to affect the flow properties and it was

Table-II: Properties of pure drug, solvent deposited acetazolamide systems, pure ingredients and blends.

Sample		Bulk density (g/ml)	Tapped density (g/ml)	Compressibility (%)	Angle of repose (degrees)
Pure acetazolamide		0.377	0.487	22.58	36.0
5% Acdisol-acetazolamide system		0.210	0.255	17.64	39.1
5% Avicel-acetazolamide system		0.188	0.222	15.31	26.0
5% Fast-Flo Lactose-acetazolamide system		0.210	0.250	16.00	38.6
Pure Acdisol		0.377	0.465	18.92	35.0
Pure Fast-Flo Lactose		0.588	0.635	7.40	14.3
Pure magnesium stearate		0.114	0.139	17.98	43.7
Formulation with 5% Acdisol system	a*	0.281	0.341	17.59	15.0
	b	0.285	0.360	20.83	39.9
Formulation with 5% Avicel system	a	0.285	0.342	16.66	16.1
	b	0.250	0.313	20.12	32.0
Formulation with 5% Fast-Flo Lactose system	a	0.312	0.367	14.98	16.5
	b	0.333	0.399	16.54	37.7

* a: without magnesium stearate; b: with magnesium stearate.

found out to be true, as seen from the data; the capsule blend with the 5% Fast-Flo Lactose system showed even better flow characteristics. The compressibility of magnesium stearate indicates a fair flow, but although it was added only in 0.5%, it changed the flow properties of the blends, among which the blend with the Fast-Flo Lactose system was affected at least. But when taking the angle of repose into consideration the flow property of this lubricant and its effect on the flow of the blends seem to be more and the data of the final blends with lubricant reflect a fair to good flow.

Table III shows that the capsules and the commercial tablets comply with the parmacopeial limits in regard of drug content, disintegration time and weight variation. Although the hardness value of the tablets was lower than the generally recommended limits of 4-7 kg (10), the mean disintegration time was longer compared to those of the capsules. The friability of the tablets were near to the limit of 0.8%, which is most likely the consequence of its low hardness.

Fig.1 and Table IV show the dissolution properties of the preparations. According to USP XXI 70% of the drug must dissolve within 45 min. The commercial tablet meets this requirement. The capsule prepared with the 5% Fast-Flo Lactose system shows a slightly better dissolution than the tablet. The formulation containing the 5% Acdisol system releases 50% of the drug within 6 min, but the best result was achieved with capsules containing the 5% Avicel system, almost 66% was released in 5 min and 90% in 12 min. Although the drug release for hard gelatin capsules was delayed for at least 2 min, which is needed for the opening of the capsules, it is obvious from the data, that the cap-

Table-III: Physical characteristics of the commercial tablet and the formulated capsules.

Preparation	Drug content (mg) (±SD)	Disintegration time (min) (±SD)	Weight (mg) (±SD)	Hardness (kg)	Friability (%)
Capsules with 5% Acdisol system	97.95(±0.95)	7.0 (±2.05)	127.18*(±0)	—	—
Capsules with 5% Avicel system	97.42(±0.75)	4.0 (±1.81)	127.18 (±0)	—	—
Capsules with 5%Fast-Flo Lactose system	99.30(±0.74)	5.5 (±1.76)	127.18 (±0)	—	—
Commercial tablet	244.44(±0.83)	14.0 (±0.75)	367.17(±3.10)	3	0.73

* The capsules were hand filled individually.

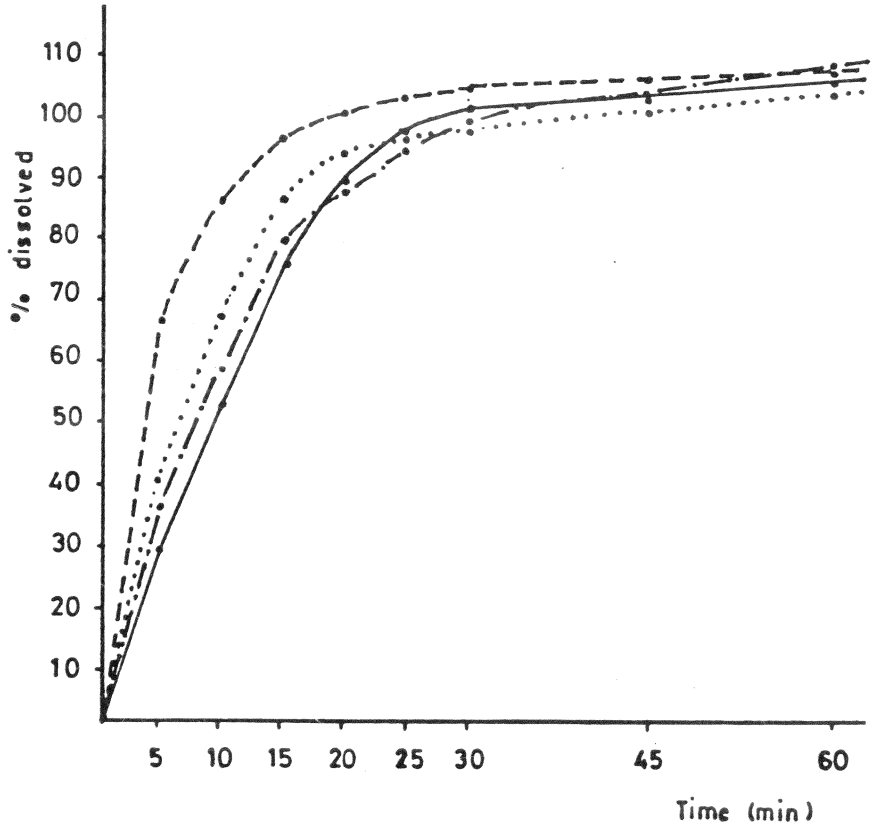

Figure 1- Dissolution profiles of the experimental capsules and the commercial tablet preparation. Key: Capsule prepared with 5% Acdisol system (.....), 5% Avicel system (- - - -), 5% Fast-Flo Lactose system (- . - . -.) and commercial tablet (——)

Table-IV: Dissolution rate data of the experimental capsules compared to the commercial tablet.

Sample	A_5 (%)	A_{45} (%)	A_{60} (%)	t_{50} (min)	t_{90} (min)
Capsule containing 5% Acdisol system	40.32	99.99	101.99	6	17
Capsule containing 5% Avicel system	65.99	103.99	101.94	<5	12
Capsule containing 5% Fast-Flo Lactose system	32.99	102.09	105.09	8	22
Commercial tablet	28.80	103.12	104.40	9.5	21

sules, especially the one with the 5% Avicel system, are superior to the tablets. The capsules can be ranked in the following order of dissolution rate: 5% Avicel system > 5% Acdisol system > 5% Fast-Flo Lactose system containing capsules. These differences stem from the solvent deposited systems themselves, which, when compared to each other, show the same order in regard of dissolution rate (4). The hydrophobic lubricant, magnesium sterate might have decreased the dissolution rate (11, 12), so changing magnesium stearate with a water soluble lubricant may enhance the dissolution rate, which will be studied further.

As a result, the study pointed out that acetazolamide capsules with a high dissolution rate could be formulated using solvent deposited systems of acetazolamide and only a low percentage of ingredients.

REFERENCES

1. Martindale- ***The Extra Pharmacopeia.*** 28th Ed., Ed. by James E.F. Reynolds, The Pharmaceutical Press, London, 1982.
2. Yakatan, G.J., Frome, E.L., Leonard, R.G., Shah, A.C., Doluisio, J.T.: ***J.Pharm. Sci.,*** **67**(2), 252-256 (1978).
3. ***The United States Pharmacopeia*** XXI. Mac Publishing Company, Easton, Pa., 1985.
4. Dortunç, B., Çolak, Ş.: Manuscript in press: ***Acta Pharmaceutica Technologica.***
5. Wells, J.I., ***Pharmaceutical Preformulation.*** Ellis Horwood Ltd., Chichester, 1988, pp. 209-211.
6. ***Turkish Pharmacopeia 1974.*** Milli Eğitim Basımevi, İstanbul, 1974.
7. USP Fast-Flo Lactose (Technical Bulletin-FMC).
8. Gissinger, D., Stamm, A.: ***Pharm. Ind.,*** **42**(2), 189-192 (1980).
9. Acdisol Faster Action (Technical Bulletin-FMC).
10. King, R.E., in ***Remington's Pharmaceutical Sciences,*** 16th Ed., Mac Publishing Company, Easton, 1980, p.1553.
11. Botzolakis, J.E., Augsburger, L.L.: ***J.Pharm. Pharmacol.,*** **36**, 77-84 (1984).
12. Chowhan, Z.T., Chi, L.H.: ***J.Pharm.Sci.,*** **75**. 542-545 (1986).

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