DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(5), 889-899 (1994)

EFFECT OF AGING ON THE DISSOLUTION RATE OF NALIDIXIC ACID TABLETS

J.K. Pandit[1], A.K. Wahi[1], S.P. Wahi[1], B.Mishra[2] and M.K. Tripathi[3]

[1]Department of Pharmaceutics, Banaras Hindu University, Varanasi-221005

[2]Department of Pharmacology, Banaras Hindu University, Varanasi-221005

[3]Drug Control Administration, Rajasthan, Alwar-301001 INDIA

ABSTRACT

Investigation of the dissolution rate profiles of nalidixic acid tablets of three commercial brands was carried out. Using the U.S.P. paddle method, significant inter-brand variations in dissolution rates were found and the tablets did not pass the U.S.P. dissolution test. The dissolution of the tablets was also found to be adversely affected on aging. The observed differences in dissolution rates of the tablets examined were unrelated to their disintegration times. An attempt was made to improve the dissolution rate of nalidixic acid tablets through hydrophilization of nalidixic acid powder and use of tablet excipients with high aqueous solubility were found to yield tablets of good physical qualities which were unaffected on aging.

INTRODUCTION

At present there are no enforced standards in India to ensure therapeutic equivalence of multisource drug products giving rise to chances of therapeutic failure.

Nalidixic acid (NA), a drug used in intractable cases of urinary tract infection, bacillary and amoebic dysentery, has an extremely low aqueous solubility and is strongly hydrophobic (1). NA tablets of various Indian manufacturers were formerly labelled as of U.S.P., B.P. or B.P.C. quality, but since 1987 all manufacturers are labelling this product as "Nalidixic Acid Tablets I.P." Only the U.S.P. specifies a dissolution minimum of 80% in 30 minutes for compressed NA tablets, no such requirement being specified in other compendia.

None of the three brands of NA tablets studied, which were labelled as U.S.P., B.P. and B.P.C., complied with the U.S.P. dissolution test. Probably to avoid the dissolution rate testing all Indian manufacturers are currently marketing their product under I.P. label. While conducting the d.t. test on these tablets it was observed that the tablets tended to float in the tubes of the U.S.P. d.t. apparatus, indicating a wetting problem, though the d.ts. of the tablets were within 15 minutes, i.e., the B.P. limit. Analysis of the tablets revealed that they were prepared with either microcrystalline cellulose or dicalcium phosphate as diluent and starch paste/ powder as granulating/disintegrating agents. Tablets containing the latter diluent showed problems in the dispersion of the granules into discrete drug particles with resultant low dissolution rates.

Moreover, all the tablets showed progressively decreasing dissolution rates.

Khalafallah et al (2) have stressed the need for prompt dissolution of nalidixic acid tablets to ensure better bioavailability. The present work involves fabrication of NA tablets which would comply with the U.S.P. dissolution standards and without the aging effect that was found in the commercial tablets studied.

EXPERIMENTAL

Materials : Nalidixic acid U.S.P., sodium taurocholate, lactose anhydrous (U.S.P.), polyvinyl pyrrolidone (m.w. 44,000) and other chemicals were purchased and were of the best quality. Elcema-P100 and lactose anhydrous were obtained as gift samples.

Nalidixic acid tablets of three brands were purchased, within two months of their date of manufacture.

Hydrophilization of NA Powder : 50 g of NA powder, passed through B.S.S. 36, was steeped in 500 ml of 10 mM solution of sodium taurocholate in a 1 liter beaker. The suspension was stirred at a low speed on a magnetic stirrer for 10 minutes. The treated powder was then filtered off on a Buchner funnel under suction and washed with 2 x 100 ml portions of distilled water. The wet mass was pressed between sheets of filter paper and finally dried at 105°C for 2 hours. The dry powder was again passed to B.S.S. 36.

Fabrication of NA Tablets : NA tablets were prepared from treated (S) or untreated (U) NA powder according to the following scheme.

1. Batches SM1 to SM4 and UM1 to UM4 contained, in each tablet, 500 mg of the appropriate NA powder,

microfine cellulose (Elcema-P100) 200 mg, potato starch 70 mg, magnesium stearate 7 mg and talc 14 mg. Tablets were made by the wet granulation method using 5, 7.5 and 10% w/v starch paste (batches 1 to 3), or 5% w/v ethanolic PVP solution (batch 4).

2. Batches SD1 to SD4 and UD1 to UD4, contained 200 mg/tablet of dicalcium phosphate dihydrate as the diluent, and other ingredients in similar quantities were incorporated as in 1 above. The same granulating agents were also used.

3. Batches ULA1 and ULA2 were made with lactose anhydrous as diluent and binders were either 5% starch paste for ULA1 or 5% w/v aqueous PVP solution for ULA2. Other ingredients were as in 1 above.

Batch size of tablets was 500. Tablets were compressed on a Manesty E2 tabletting machine using 7/16" standard concave punches. The machine was adjusted to yield tablets of 5 hardness units (Monsanto hardness tester). The tablets were stored in securely capped, wide mouth amber coloured bottles.

All tablets, both commercial and fabricated, were subjected to hardness, friability, d.t., weight variation, content and dissolution test according to USP XX monograph. The commercial tablets were evaluated within 2 months of manufacture, and one and four years thereafter. The fabricated tablets were evaluated within 24 hours of compression and after one and four years. At least five replicates were run for all tests. Instead of the one point sampling at 30 mts of dissolution test specified in the USP aliquots were withdrawn at 5 minute intervals up to 30 minutes. All dissolution samples were analyzed on a Beckman 24 spectrophotometer at 259 nm. A calibration curve

prepared from U.S.P. Nalidixic Acid RS in 0.01 N sodium hydroxide solution was used to calculate the actual concentration of NA in the samples.

RESULTS AND DISCUSSION

The hardness of the fresh fabricated tablets was between 4.5 and 5.5 units. After storage the hardness of all fabricated tablets varied within ±0.5 units of the initial value, and thus no cognizable change in this parameter was observed. Of the three brands of commercial tablets two had similar hardness values at 1 and 4 years of 5.1 and 5.0 units, respectively, but a steep increase in the hardness of brand 3 tablet was observed after storage, the initial, 1 and 4-year values being 4.5, 8.5 and 10.8 units, respectively. Incidentally, this tablet showed the maximum effect of aging on dissolution rate.

In comparison to hardness more changes in the friability was observed after storage. While batches SM1 to SM4 showed the lowest fribaility (< 0.1%), batches made with untreated NA and/or dicalcium phosphate showed higher friability values, and batches UD1 to UD3 did not pass the test. All other batches, including the commercial tablets, passed this test and no aging effect was seen. The friability of tablets made with PVP solution as binder showed lower values than tablets made with starch paste.

In the present investigation a clear effect of excipient on disintegration time (d.t.) is observed in some batches, while in some no clear effect is seen (Table 1). All tablets disintegrated within 15 minutes (official limit), but those made with 10% starch paste show higher d.t. values than those made with 5 or 7.5% starch paste. Batches prepared with PVP

TABLE 1

Disintegration Time of Fresh, One And Four Year Old Fabricated And Commercial NA Tablets

Batch	D.T. in Minutes		
	Fresh	One year old	Four year old
SM1	3.5	3.6	3.3
SM2	7.5	9.1	8.3
SM3	13.0	9.0	9.0
SM4	1.4	1.3	1.3
SD1	3.3	3.5	3.6
SD2	4.5	5.0	5.1
SD3	7.3	9.0	9.1
SD4	1.4	2.1	1.9
UM1	4.4	4.4	4.5
UM2	5.5	5.4	6.3
UM3	15.0	15.0	15.0
UM4	2.5	2.5	2.3
UD1	4.5	4.5	4.4
UD2	7.3	8.0	8.0
UD3	8.5	8.6	8.5
UD4	3.6	3.4	3.5
ULA1	8.5	7.9	6.3
ULA2	6.5	6.4	6.2
Brand 1	2.6	4.7	4.5
Brand 2	2.5	9.5	9.5
Brand 3	2.0	2.7	8.5

solution showed very low d.t. values, except batch ULA2, which did not differ appreciably from ULA1, prepared with 5% starch paste. Surface treatment of NA was beneficial in reducing the d.t., as is seen in batches SM4 and SD4 versus UM4 and UD4. The drug content observed in all the tablets, initially and 1 and 4 years after storage, was within the official limit.

The dissolution rates of the tablets are recorded in table 2 as times for different percentages of NA dissolved in USP dissolution medium. Tablet SM4 complied with the U.S.P. dissolution test at all stages of testing, whereas SM1, SM2 and SM3 failed the test. None of the tablets made with dicalcium phosphate passed the test. It is obviously because of the diluent, in that dicalcium phosphate forms very strong intragranular bridges, thereby impeding dissolution by preventing the formation of primary drug particles. Even an extremely hydrophilic binder like PVP is unable to exert much osmotic pressure on these tablets when put in the dissolution medium, so that discrete drug particles could not form.

The effect of aging is more pronounced in tablets made with untreated NA powder. Only fresh UM4 tablets met the U.S.P. dissolution requirement, decreasing to 77.4% and 73.4% after one and four years, while the dissolution from fresh UM1 and UM2 and UM3 tablets varied between 9 and 29% at 30 minutes. The aging effect is more pronounced in the latter batches.

The very poor dissolution of tablets UD1 to UD4 is noteworthy. None of the tablets could even marginally reach the U.S.P. minimum. Of the three batches made with starch paste only fresh tablet UD3

TABLE 2

Dissolution Rates of Fabricated and Commercial NA Tablets

Batch	Amount Dissolved in 30 mts, %			$T_{25\%}$, mts.			$T_{50\%}$, mts		
	Fresh	1 yr.	4 yr.	Fresh	1 yr.	4 yr.	Fresh	1 yr.	4 yr.
SM1	76.2	73.2	69.3	6.5	4.5	8.7	13.5	14.5	17.5
SM2	62.2	53.5	43.3	9.8	11.6	16.7	25.0	29.0	-
SM3	52.2	42.3	36.5	12.5	8.5	14.3	28.3	-	-
SM4	90.2	82.0	82.3	1.7	2.5	3.2	3.3	3.4	4.3
SD1	30.7	14.9	13.5	25.7	-	-	-	-	-
SD2	18.6	14.3	12.6	-	-	-	-	-	-
SD3	19.2	12.0	13.5	-	-	-	-	-	-
SD4	62.3	45.5	42.4	4.2	8.3	9.8	14.8	-	-
UM1	29.2	20.4	15.3	25.2	-	-	-	-	-
UM2	14.3	14.0	10.5	-	-	-	-	-	-
UM3	8.9	10.2	8.2	-	-	-	-	-	-
UM4	81.4	77.4	73.5	2.3	3.0	3.1	4.8	6.8	8.8
UD1	13.2	15.2	11.6	-	-	-	-	-	-
UD2	9.8	8.2	9.3	-	-	-	-	-	-
UD3	29.4	18.2	14.2	20.0	-	-	-	-	-
UD4	75.8	61.2	55.3	3.0	4.0	4.1	8.0	18.3	23.5
ULA1	8.9	7.8	9.6	-	-	-	-	-	-
ULA2	95.7	93.6	93.3	3.5	3.3	3.4	9.0	9.1	8.8
Brand 1	71.4	72.0	66.5	4.3	5.5	4.5	16.3	18.3	21.6
Brand 2	77.9	69.5	61.2	5.5	3.5	5.5	15.1	18.8	24.5
Brand 3	60.3	48.6	43.8	8.2	9.6	15.3	22.6	-	-

- indicates the level did not reach. Mts - minutes

reached 25% dissolution, and the dissolution rate reduced drastically with aging. The possibility of an interaction between NA and dicalcium phosphate resulting in the formation of a highly insoluble layer of the calcium salt of NA seems to be one of the main reasons for the uniformly poor dissolution rate of NA tablets made with this diluent.

The dissolution rate of tablet ULA1 is very poor at all stages, but the dissolution rate of tablet ULA2 is truely noteworthy, in that at least 90% of the drug is dissolved in 30 minutes at all the stage of aging.

Usually a formulator aims at making his finished tablet to disintegrate as rapidly as possible for rapid onset of action and full physiological availability. Surfactants can be very effective in improving tablet disintegration when spread onto granules (3). The surfactant here acts as a wetting agent, which lowers the advancing contact angle and aids in displacing an air phase at the surface and replacing it with a liquid phase and also lowering the surface tension, which tends to decrease the coefficient of penetration (4). According to Nogami et al. (5) the rate determining step in tablet disintegration is the process of water penetration into the tablets via the pores. The process of separation of particles is a much faster process than the process of water penetration. Any material or any process that shortens the process of water penetration would decrease the d.t. and increase dissolution rate.

Heng et al. (6) have suggested that the size of the disintegrated particles have a dominant influence on drug release from tablets. Thus, an excipient capable of producing finer dispersion of disintegrated

particles would enhance drug release through the increased surface area of dissolution. In the present study the treatment of NA powder with sodium taurocholate leaves only traces of the surfactant on the drug crystals, hence this treatment can only be expected to induce more wetting. Moreover, the possible formation of an alkaline micro-environment during wetting of the sodium taurocholate-treated NA powder, through which NA may have replaced taurocholate in the sodium salt to form the sodium salt of NA, which is of much higher solubility than NA, will further act as dissolution enhancer by promoting water penetration into the tablets and causing quicker formation of primary drug particles. Shah et al. (7) have shown that soluble excipients give the fastest drug release. Thus, PVP and lactose anhydrous as highly soluble excipients ensure quick release of the drug substance. These excipients are quickly dissolved out from the tablet matrix resulting in the quick formation of primary drug particles with consequent high dissolution rates. However, PVP alone is not as efficient alone, as it is in combination with lactose anhydrous when untreated NA is used. For the treated drug, granulation with PVP is sufficient to ensure quicker dissolution rate which passes the U.S.P. test up to four years of aging.

In conclusion it may be said that there is a genuine need to examine the effect of aging on NA tablets, and its effect on the physiological availability of NA. This part of the study will be communicated in a later report.

ACKNOWLEDGEMENTS

The generous gift of Lactose Anhydrous by DMV, Holland and of Elcema-P100 by Degussa, Frankfurt, is gratefully acknowledged. The authors also thank Prof. Mounir S. Mesiha, Alfred & Mary Scwartz College of Pharmacy, New York, for some very stimulating discussions.

REFERENCES

1. N.A. El-Gindy, A.A. Shalaby and M.M.A. El Khalek, Drug Dev. Ind. Pharm., 89, 683 (1982).
2. N. Khalafallah, M. Darwish and S.A. Khalil, Drug Dev. Ind. Pharm., 8, 579 (1982).
3. B.F. Cooper and E.A. Brecht, J. Am. Pharm. Assoc., Sci. Ed., 46, 520 (1957).
4. H. Nogami, H. Fukuzawa and Y. Nakai, Chem. Pharm. Bull. 11, 1389 (1963).
5. H. Nogami, J. Hasegawa and M. Muramoto, Chem. Pharm. Bull., 15, 279 (1967).
6. P.W.S. Heng, L.S.C. Wan and T.S.H. Ang, Drug Dev. Ind. Pharm., 16, 951 (1990).
7. N. Shah, R. Pytelewski, H. Eisen and C.I. Jarowski, J. Pharm. Sci., 63, 339 (1974).