DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(15), 2449-2457 (1994)

Pharmaceutical Characteristic Difference of Several Kinds of Nitroglycerin Tablets

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SUMMARY

In recent years, Nitroglycerin(NG) has been reevaluated as to its usefulness against angina pectoris. A number of new dosage forms of NG have been developed by pharmaceutical companies. However, there is still a great demand for NG sublingual tablets as a specific medicine to deal with angina pectoris attacks. NG has a high volatility, so patients need to pay attention to the handling and carrying of NG tablets. Recently, new NG tablets have been manufactured by several companies. These NG tablets are designed to either prevent or retard NG volatility from the NG tablet.

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Newly designed tablets, Nitrostat(NS), Nitropan(NP) and conventional nitroglycerin tablets (Yamakawa(YK)) were examined to elucidate their pharmaceutical characteristics. The characteristics examined were as follows: measurement of remaining quantity of NG after various storage conditions, hardness test, friability test, content uniformity test and disintegration test. As a result, NP was superior for its ability to prevent NG volatility as compared to NS and YK under all experimental conditions tested. NP also gave excellent results for all analyses.

INTRODUCTION

NG tablets have been used for many years as a specific medicine to deal with an angina pectoris attack. Patients can not predict their angina pectoris attack so they constantly carry NG tablets. NG tablets should be produced with regard to this point. Based on the above considerations, the present study was planned to investigate the pharmaceutical characteristics of NG tablets noting the preventing effect of NG volatility from NP and NS. In order to estimate the preventing effect by film packaging, YK, NP and NS were also studied using the same testing under several different film packaging conditions. The NG tablets used and their pharmaceutical features are listed in Table I. A distinctive feature of the NS tablet and NP tablet is that they contain dextran and β-cyclodexrin(β-Cyd), respectively.

Experimental

Materials Yamakawa®(YK) and Nitropen®(NP) Nitroglycerin tablets were obtained from Nippon Kayaku Co., Ltd. Nitrostat®(NS) was kindly supplied by Warner

Lambart K.K. The other materials used were of reagent grade.

Disintegration Test The disintegration test was done using a Toyama Sangyo NT-2 type disintegration tester according to the method in Japanese Pharmacopeia XII, but the attached disk was not used. Purified water was used as the disintegration medium.

Friability Test Tablet friability was obtained from the decrease in weight of 20 tablets after 100 rotations using a Kayagaki Irikakogyo friabilator at 25rpm. In addition, tablet friability for long periods were also observed from the decrease in weight of 30 tablets after 60 minutes using a friabilator at 26rpm.

Hardness Test The hardness of the tablet was measured using a hardness tester (Type TS-50N; Okada Seiko Co., Ltd.). Every test was carried out using 6 tablets.

Content Uniformity of NG The NG content uniformity of each tablet was determined using high performance liquid chromatography (HPLC). The HPLC conditions were as follows: A Jasco Model 800 system equipped with a variable-wavelength U.V.detector; column, FAINPAK $_5C_{18}$ (4.2mm i.d.X150mm); mobile phase,methanol-water(55:45); flow rate 1.2ml/min; and detection, 210nm.

Stability of NG tablets versus heat under several packaging conditions. Non-packed tablets, packed tablets with cellulose films on both sides, packed tablets with a combination of a cellulose film and a metal film on each side and packed tablets with a

metal film on both sides were assembled before the stability experiment. The stability of NG tablets versus heat was investigated by placing them in a desiccator at 25°C, 40°C and 50°C. Five tablets were withdrawn at appropriate intervals and prepared for analysis in the following manner. The tablets were transferred to a 20ml volumetric flask containing 2ml purified water and 1ml internal standard solution [0.1% p-Aminobenzoic acid n-propyl ester ethanol solution], and dispersed into about 15ml of ethanol with shaking. Complete disintegration of the tablets in the ethanol was achieved by sonication for 5min. The volume of the dispersion was adjusted to 20ml with ethanol. It was then centrifuged at 5000rpm for 5min, and 1ml of supernatant was pipetted and filtered through a membrane filter (4μm). Twenty μl of the filtrate was subjected to HPLC for NG determination under the HPLC conditions already described.

RESULTS AND DISCUSSION

The size and remarkable features of the tablets are shown in Table I. Their weight and volume were in the order of NP>NS>YK. The mean hardness value of the tablets was NP=1.8Kg, NS=1.2Kg and YK=0.8Kg, respectively. Coefficient of variation(CV) for the hardness test was YK=0.25, NP=0.18 and NS=0.29. NP had the smallest CV. In contrast, NS had the largest CV value. The friability test showed the rate of weight decrease in the order of NS>YK>NP. The rate of friability of NS was significantly large, and showed a 2.18% decrease after one hundred rotations. On the other hand, NP and YK only showed respectively a 0.04% and 0.38% decrease under the same conditions. The rate of friability of a tablet under a load of 26rpm for

Table I Nitroglycerin tablets in this study

commercial name / item	Nitroglycerin Tablet(Yamakawa®*)	Nitropen®	Nitrostat®
appearance	white tablet D.4.1mm X T.2.3mm	white tablet D.5.0mm X T.2.4mm	white tablet D.4.1mm X T.2.3mm
content	glyceryl trinitrate 0.3mg/1T	glyceryl trinitrate 0.3mg/1T	glyceryl trinitrate 0.3mg/1T
composition of bulking agents	lactose corn starch acacia talc	β-cyclodextrin lactose crystalline cellulose corn starch polyvinylpyrrolidone magnesium stearate	polyethylene glycol 3350 lactose sucrose
package	amber glass bottle, gum cap 20T X 5bottle	metal strip pakaging 10T X 10sheet	amber glass bottle, metal screw cap 100T X 1bottle
storage	Store in light-resistant, tight containers at a temperature not exceeding 20°C.	Store in light-resistant at room temperature	Store in light-resistant, tight containers at room temperature
warning for using	Tighten cap immediately after taking out the tablet. Please fill in the beginning date of use on the bottle, because the drug content might be decreased after more than 3 months after first opening	none	dispense in original unopened container

*This is a conventional nitroglycerin tablet in Japanease market.

30minutes resulted in approximately 20% for NS, approximately 5% for YK and less than 1% for NP. NP showed an extremely small friability, so this characteristic has the advantage of permitting much easier handling and carrying of the NG tablets by patients. The disintegration time was short and in the order of YK<NP<NS. The disintegration time for NS which took only 3.3seconds was especially rapid in comparison to NP(=25s) and YK(=49s).

There was no relationship between the hardness and disintegration time of tablets in this experiment. This result might be affected by a difference in each tablet's binding agents . According to the content uniformity test, NS and YK showed a similar distribution in their content uniformity. NP showed a smaller variance than the other tablets in their distributions. Their average contents were NP=0.334mg/T, NS=0.308mg/T and YK=0.306mg/T. Using the comparison of CV, both NS and YK were 0.051 while NP was only 0.017.

The above difference may have resulted from a retention of the NG content of NP at the time of manufacture, because NP significantly prevented NG volatility. This speculation is consistent with the results obtained for the stability of NP during storage by Sekigawa et al[2].

The stabilities of YK, NP and NS were examined under several different conditions. Figure 1 shows the stabilities of YK, NP and NS at 40°C under a non-packaged condition. The NG remaining in NP tablets was 99.98% after 4 days stand. Those of NS and YK under the same condition were 25.5% and 18%, respectively. The NG remaining in NP, NS and YK at 25°C were 91%, 22% and 16% after 14 days standing, respectively. The NG remaining in NP, NS and YK at 50°C

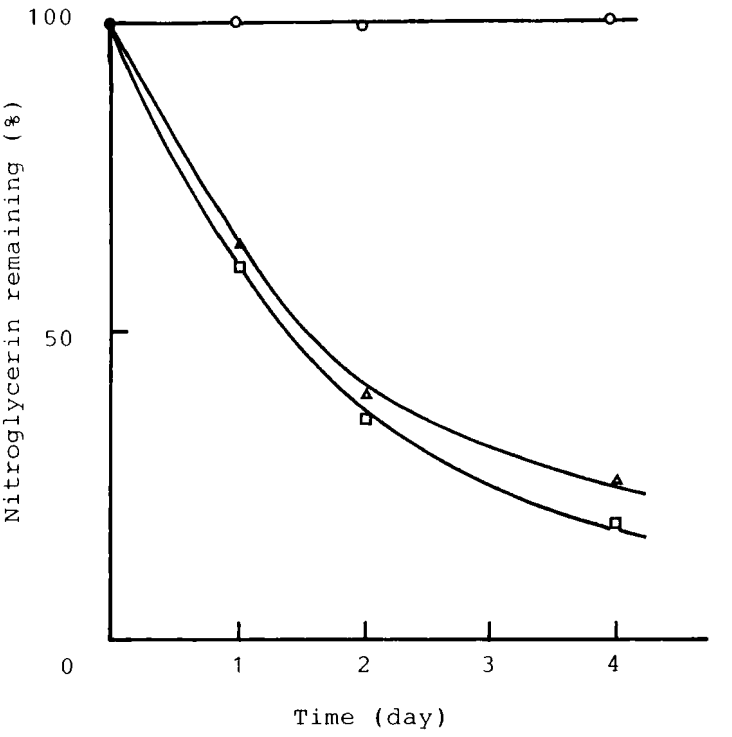

Figure1 Loss of Nitroglycerin at 40°C from Non-packed Tablets

○:Yamakawa® Nitroglycerin Tablet
□:Nitropen®
△:Nitrostat®
Each point represents the mean of 5 tablets.

were 99%, 54.5% and 26.5%. The loss of NG from packed NP using a metal film on both sides was less than 2% at 40°C after 2 months stand. On the other hand, the NG remaining in NS and YK under the same condition was 74% and 32%. The loss of NG from tablets packed using metal film on both sides showed the same tendency at different temperatures(25 and 50°C). The NG remaining in packed NP using cellulose film and metal film on

each side was 96% at 40°C after 2 months stand. The NG respectively in NS and YK under the same conditions was 58% and 0%, remaining. The loss of NG from packed tablets with cellulose film and metal film on each side showed the same tendency at different temperatures(25 and 50°C). The NG remaining in packed NP with cellulose film on both sides was 56% at 40°C after 2 months stand. The NG remaining in NS and YK under the same condition was 38% and 0%. The loss of NG from packed tablets with cellulose film on both sides showed the same tendency at different temperatures(25 and 50°C).

NP showed an excellent preventing effect for NG volatility under all conditions used in these experiments. In particular, NP contained in an aluminum strip package resulted in the almost perfect prevention of NG volatility. The preventing effect was observed for NS in comparison with YK, but that of NS was not as effective as that of NP. In addition, the degree of prevention of NG volatility by NS depended upon the storage conditions. Thus, prevention of NG volatility by NS was not observed in non-packaged conditions. However, NS could prevent NG volatility for any packaging condition. However, the air-tightness condition did show some volatilization prevention. These results are in agreement with the data reported by M. Lagas et al[3]. The above results showed that the use of β-CD as an additive had an advantage over other additives with regard to stability and strength of the NG tablets. The exact mechanism of the β-CD/NG interaction is not discussed in this paper. Extensive studies concerning the cyclodextrins/NG interaction have been reported elsewhere[4].

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