East and Central African Journal of Pharmaceutical Sciences
3(2000) 61 - 65

Physico-Mechanical Properties of Processed Hydrogenated Vegetable Oil Matrices

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The present study was aimed at improving the physico-mechanical properties of hydrogenated vegetable oil (HVO) matrices. HVO was processed with a variety of binders plus an auxiliary binder, stearic acid. The resulting formulations were fractionated into a variety of particle sizes while some were made into a fixed blend. Tensile testing and dissolution studies were carried out on the various compacts prepared.

The minimum amount of binder, PVP K-30, that imparted appreciable tensile strength to the processed HVO matrices was about 7% w/w. At PVP K-30 concentrations above 7.5% w/w, the release sustaining characteristics of the matrix significantly depreciated ($t_{cal} \geq 5.13$, $t_{tab} = 2.23$, $p=0.05$), even though tensile strength significantly improved. Besides retaining the basic release sustaining characteristics of the matrix, PVP K-90 and Luviskol proved to be a better binder than PVP K-30 ($t_{cal}=5.22$, $t_{tab}=2.05$, $p=0.05$) PVP K-30 and Luviskol produced tablets with the same release sustaining characteristics ($t_{cal}=0.05$). Large particles (500-710 μm) produced compacts with the best release sustaining characteristics and tensile strength.

The present study showed that the tensile strength of HVO matrices can be improved by processing the HVO with an auxiliary binder such as stearic acid. Controlled release efficiency and tensile strength of such matrices can be enhanced by using large particles, (500-710 μm), of the formulation.

Key words: Hydrogenated vegetable oil, controlled release efficiency, tensile strength.

INTRODUCTION

Hydrogenated vegetable oils (HVO), like other hydrophobic inert materials, form monolithic sustained release delivery systems that release drug over prolonged periods of time [1]. However HVO tablets have poor mechanical properties and they tend to stick excessively to tablet tooling [2]. In order to improve tablet strength, a binder is usually added during the granulation process. Another important factor that determines the strength of the tablets is the particle size of the granulation/powder from which the compacts have been made [3-5]. In general, smaller particles produce stronger compacts than larger ones due to the availability of larger areas of true contact on the former than on the later [6-7]. Enhanced release sustaining characteristics are also expected with tablets made from smaller particles due to decreased porosity. The magnitude of the compacting load also greatly influences compact strength and release efficiency in the case of sustained release matrices such as HVOs. The compacting load increases the area of true contact between particles thereby affecting ultimate compact strength and porosity [5]. In HVO and other relatively low melting point substances, besides this, compaction force affects the extent of the partial melt-fusion phenomenon which is believed to be partly responsible for the strength and controlled release efficiency of such matrices.

As mentioned earlier, HVO compacts posses poor mechanical properties and hence this study was aimed at improving these properties utilizing the factors discussed above.

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MATERIALS

Sterotex K (hydrogenated castor oil) Aston Chemicals, UK, was the HVO that functioned as the basic release sustaining hydrophobic matrix material. *PVP K-30 and K-90* (polyvilpyrrolidone), supplied by Dykem Chemicals, UK were employed as binders. *Luviskol* (polymer of PVP and polyvinyl acetate), supplied by BASF, Germany was used as a binder. *Polyplasdone KL-10* (cross-linked PVP), supplied by GAF Chemicals, USA was also used as a binder. Stearic acid supplied by Sigma Chemical Company, USA was used as an auxiliary binder. *Propranolol hydrochloride* supplied by Industrie Chimiche, Italy was used as the drug of choice in assessing the release characteristics of the HVO matrix.

METHODS

Preparation of Processed HVO

The HVO, Sterotex K was processed with a binder and an auxiliary binder, stearic acid. The binder used was either Luviskol, polyplasdone, PVP K-30 or K-90. All the binders except PVP K-30 were used at one concetration, 7.5% w/w. PVP K-30 was used at concetrations ranging fromm 0-30% w/w while stearic acid was used at 5% w/w concentration. The binder was gradually dissolved or dispersed in water with the aid of heat (60°C). The volume of water used in each case was equivalent to 20% v/w of the total processed HVO. Molten stearic acid was gradually added to the aqueous binder solution or suspension while stirring vigorously. The resulting warm, stable dispersion was gradually added to the HVO in a high-speed mixer granulator (Kenwood, Type FP600, Kenwood Ltd., UK). The mixture was granulated for about 2 minutes before being tray dried overnight in a convective oven (Baird and Tatlock Ltd., UK). All the formulations were passed through a 710 μm process sieve and then fractionated using test sieves into the following particle size ranges: 500-710 μm, 355-500 μm, 250-355 μm, 180-250 μm and <180μm. The various particle sizes of processed HVO were dry mixed with the drug, propranolol hydrochloride (ratio 110:40 respectively). In some cases the various size fractions were reconstituted to a fixed particle size distribution before dry blending with the drug (ratio 110:40). The fixed particle size distribution was as follows: 500-710μm = 25%; 355-500μm = 35%; 250-355=25%; 180-250μm =10% and <180μm =5%.

Preparation of Tablets

Tablets were made using a manually operated instrumented Manesty E2 tablet press equipped with 8 mm flat faced punches. Tablets were approximately 150 mg and were made at forces ranging from 3 to 18 kN. Formulation samples weighing 150.2-150.3 mg were manually fed into the die before compaction.

Dissolution Testing

Dissolution was carried out 24 hours post compaction according to the USP dissolution method II. A mean of 6 tablets was used.

Tablet Tensile Strength Measurement

Tablet strength evalution was carried out 48 hours post compaction using a tensile tester (Type T5000, JJ Lloyd Instruments, Ltd., UK). Tablet radial tensile strength, (Ts) was calculated from the following equation: $Ts=2F_c/\pi dt$, where F_c is the diametral crushing force, d is the tablet diameter and t the tablet thickness. A tensile strength mean of 15 tablets was used in this study.

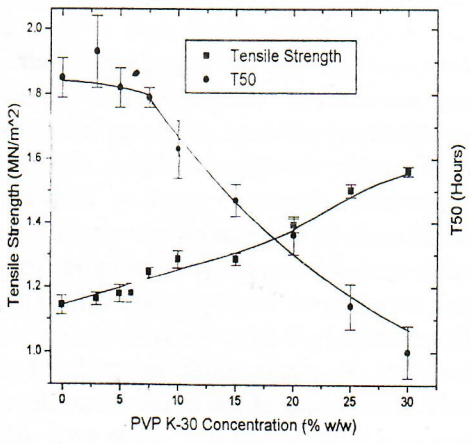
RESULTS AND DISCUSSION

Fourmulation changes were studied in relation to release sustaining characteristics (controlled release efficiency). These characteristics could be inferred from the time for 50% drug release (T50) and they were directly related to this variable. Statistical analysis performed on some of the data obtained includes student-t tests and one way analysis of variance with results evaluated at 5% significant level (p-0.05). The calculated t values, t_{cal}, F values, F_{cal}, and statistical tables' t values, t_{tab} and F values, F_{tab}, at the appropriate degrees of freedom at p=0.05 are quoted in the text. All error bars figures are standard error of mean.

The effects of binder (PVP K-30) concentration on tensile strength and release sustaining characteristics of the compacts made from processed HVO are summarized in figure 1. The compaction force in both cases is 12 kN. Increase in binder concentration resulted in an increase in tensile strength of the compacts. This is in agreement with literature reports that show that high binder concentrations produce granules of higher strength than low ones [8,9], hence strong tablets. However, tablets made from 0-6% binder concentration had the same radial tensile strength (F_{cal} = 0.51, F_{tab}≈2.76): hence the minimum PVP K-30 concentration that imparted appreciable tensile strength to the HVO matrix was approximately 7% w/w.

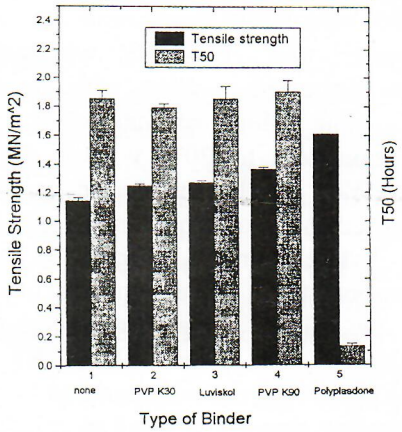
As tensile strength improved, release-sustaining characteristics gradually depreciated (Figure 1). This was attributed to the hydrophilic nature of PVP K-30. PVP K-30 probably enhanced drug release by acting as a channeling agent. However, matrices containing 0-7% binder had the same release sustaining characteristics (F_{cal}=0.73, F_{tab}=2.76). Above 7.5%, release sustaining characteristics significantly depreciated (t_{cal}≥ 5.13, t_{tab}=2.23): therefore the maximum amount of PVP K-30 that could be incorporated into the HVO matrix to improve tensile strength without affecting controlled release efficiency was approximately 7% w/w.

Figure 1: The effect of binder concentration on tensile strength and controlled release efficiency



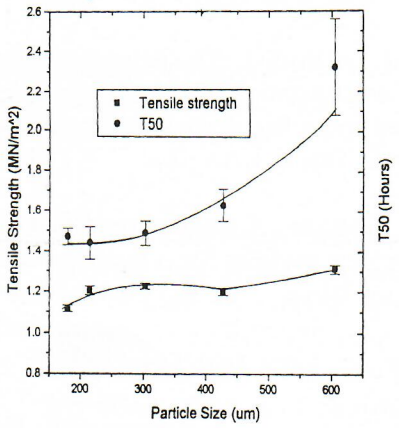
The summary of the effect of the type of binder on tensile strength and release sustaining characteristics is shown in figure 2. All the tablets in this case were made at approximately 12KN. Besides retaining the basic release sustaining characteristics (t_{cal}=0.52, t_{tab}=2.23), tablets containing PVP K-90 had superior strength to those containing PVP K-30 (t_{cal}=5.22, t_{tab}=2.05). This was probably due to the higher relative molecular weight of the former than the later. However, like PVP K-90, PVP K-30 had negligible effect on release sustaining characteristics of the HVO matrix. Polyplasdone produced tablets with the best tensile strength but it totally destroyed release sustaining characteristics. Although insoluble in water, polyplasdone is very hydrophilic and upon absorption of water its lattice structure expands and ruptures the HVO matrix. PVP K-30 and Luviskol produced tablets with the same tensile strength (t_{cal}=0.80, t_{tab}=2.05) and release sustaining characteristics (t_{cal}=0.61, t_{tab}=2.23). However, Luviskol unlike PVP is a co-polyster which is not very stable, consequently, PVP K-30 is to be preferred over Luviskol.

Figure 2: Effect of type of binder on tensile strength and controlled release efficiency



The effect of particle size on compact strength and release sustaining characteristics is summarized in figure 3. In both cases the compaction force was 12kN and the formulations were made from the various size fractions plus the drug in the ratio 110:40 respectively.

Figure 3: Effect of particle size on tensile strength and controlled release efficiency

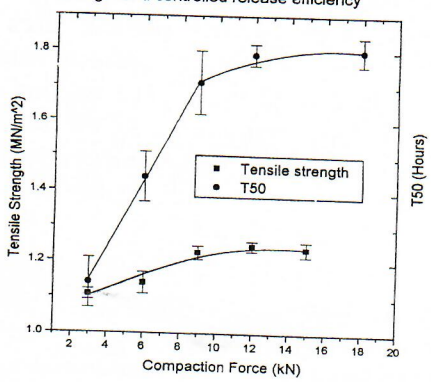


In general, tablet strength was found to increase with an increase in particle size. The three medium particle sizes, 180-250μm, 250-355μm and 355-500μm, produced tablets with the same tensile strength (F_{cal}=0.70, F_{tab}≈3.23). There was significant difference in the strength of tablets made from the smallest particles, <180μm, and that of tablets made from the three medium particle diameters (t_{cal}≥3.49, t_{tab}=2.05). Further significant difference in compact strength exists between compacts made from the three medium particle size ranges and those made from the largest particles, 500-710μm (t_{cal}=3.14, t_{tab}=2.05). The above trend was almost mirrored by the effect of particle size on release sustaining characteristics of the tablets. The main difference is that matrices made from the smallest particles, <180μm, had the same release sustaining characteristics as matrices made from the three medium particle size ranges, 180-250μm, 250-355μm, and 355-500μm, (F_{cal}=1.50, F_{tab}=3.10). However, tablets made from the largest particles, 500-710μm, had significantly superior release characteristics to those made from the rest of the particle size ranges (t_{cal}≥5.68, t_{tab}=2.23).

The larger particles had higher initial die fill volumes compared to the smaller particles prior compaction. This probably resulted in a higher deformation potential [3] for the former than the latter that contributed to strong compacts. Usually tablets made from different particle sizes have different release sustaining characteristics as obtained in the present study. The fraction of the upper punch force transmitted to the stationary lower punch (R value) was significantly higher with larger particles than with smaller ones. For example: R=0.893±0.004 for 500-710μm particles: R=0.888±0.008 for 250-355μm particles (t_{cal}=2.16, t_{tab}=2.05). This was possibly due to a decrease in the area of true contact between the die wall and large particles in comparison to small particles. This reduced the overall particle die wall friction and maximized the force transmitted to the lower punch in the case of the large particles. In general, there is an increase in the force per unit area (pressure) upon compaction of large particles than small particles due to the smaller specific surface area on the former than the latter. This probably results in more partial melt-fusion of the low melting point HVO contained in the large particles than in the small ones. The cold welding phenomenon will thus produce more bonds in tablets made from large particles than those made from small particles as obtained in the present study.

The effect of compaction force/load on tablet tensile strength and release sustaining characteristics is summarized in figure 4. These tablets were made from the fixed blend formulation plus the drug (propranolol hydrochloride) (ratio 110:40). Compact strength and release sustaining characteristics were found to increase with compacting load to a maximum value. The minimum force required to produce maximum tablet strength and release sustaining characteristics was approximately 9kN. At 9kN the tablets probably achieved minimum porosity hence maximum release sustaining characteristics. High compaction forces increase inter-particulate true contact and in low melting point materials such as HVOs, besides this, high forces also enhance the partial melt-fusion phenomenon, thereby improving compact strength.

Figure 4: Effect of compaction force on tensile strength and controlled release efficiency



CONCLUSION

From this study it was concluded that HVO compact strength can be significantly improved by processing the HVO with binders and an auxiliary binder. However, hydrophilic binders reduce the controlled release efficiency of the HVO matrix: hence it would be advantageous to incorporate hydrophobic inert binders with strength imparting properties such as those of polyplasdone. Compact strength and controlled release efficiency can be reinforced and ehnanced respectively by using large particles, 500-710μm, of processed HVO. This was attributed to: high deformation potential of large particles; high fraction of upper punch force transmitted to the lower punch for large particles and high per unit area transmitted in the case of large particles. These factors were thought to enhance the partial melt-fusion phenomenon within the compacted tablet and this enhanced compact strength and controlled release efficiency. The minimum force required to produce maximum strength and release characteristics was approximately 9kN.

ACKNOWLEDGEMENT

We would like to thank the University of Zimbabwe and the British Council for sponsoring this research.

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