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COMMUNICATIONS

EVALUATION OF EGG ALBUMIN AS A FILLER FOR PROLONGED RELEASE DIRECT COMPRESSED TABLETS

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Abstract

Direct compressed tablets for drugs of different physico-chemical properties were prepared using egg albumin as tablet filler. The prepared tablets at different drug:egg albumin ratios as well as the powder blends used for the preparation of the tablets were evaluated. The drug dissolutions from the egg albumin tablets were slow and different release profiles were obtained depending on the type of the drug. The release kinetics from the albumin matrix were tested for different models and were found to be anomalous resembling release of drugs from swellable type of matrices. In order to elucidate the release mechanism, the interaction of drugs with egg albumin was examined by thermal analysis. In most cases release retardation was increased with the increase of egg albumin matrix density. In case of meclizine-HCl the release was not depending on the egg albumin matrix density and it was believed that the rate determining step for its release is drug solubility and/or dissociation of the drug-egg albumin complex.

Introduction

Direct compression as the process by which tablets are compressed directly from powder blends of active ingredients and suitable compressible excipients has the advantages of economy, elimination of heat and moisture problems in addition to stability of the final product (1).

Egg albumin is available as dry powder, it is widely used in the field of foods and pharmaceutical formulation. As a natural polymer, it has recently attracted considerable attention in pharmaceutical field due to its safety. Egg albumin has been evaluated as drug carrier and its effect on drugs dissolution was studied for different oral formulations such as solid dispersion (2, 3) and microcapsules (4).

The aim of the present study was to evaluate egg albumin as a filler for the preparation of direct compressed tablets. The dissolution of selected drugs from the formulated egg albumin tablets was also characterized.

Experimental

Materials

Egg albumin was purchased from BDH Chemicals Ltd. (Poole, England). Salbutamol sulfate (Glaxo Co., U.K.), theophylline (Merck Co., Darmatsdt, Germany), meclizine hydrochloride and aminophylline (Winlab Ltd., Maidenhead-Berkshire, U.K.) were used as received. All other reagents and solvents were of analytical grade.

Preparation of Tablets

Drug contained tablets were prepared using powdered drugs and excipients that pass through 120 μm sieves. Drug, egg albumin powder and 2% magnesium stearate were mixed together for five minutes in a high speed mixer (Erweka-Apparatebau, Turbula, System S27, Germany).

Tabletting was proceeded on powder blends using direct compression (Erweka-Apparatebau, Eko, Germany). All tabletting was conducting in a room where temperature and relative humidity maintained at 22 ± 1°C and 35 ± 5%, respectively. The same circular, flat-faced punch and die was used for tabletting of each drug at different drug-egg albumin ratios to help minimizing tooling errors and constant compression force. The die was hand-filled with pre-weighed powder sample to ensure constant compression force as well as amount of drug in each tablet.

Compressibility and flowability

Powder blends of drug with egg albumin at different ratios were subjected for compressibility measurement using the equation (5),

$$\% \text{ Compressibility} = (P_t - P_o) / P_t \times 100$$

where Pt is the tapped bulk density and Po is the initial bulk density. The compressibility data allowed for the characterization of the powder flowability using Jones T.M.'s tables (6).

Tablet Crushing Strength and Disintegration

The prepared direct compressed drug-egg albumin tablets were tested for their crushing strength immediately after compression using a motorized tablet hardness tester (Erweka, TBH 28, Germany). For each determination ten tablets were tested and the mean crushing strength in kilopounds (kp) was determined.

Tablet disintegration was tested at 37°C in simulated gastric fluid (7) using an Erweka Disintegrator (Erweka-Apparatebau, ZT4, Germany). The tests were performed without disks.

In-Vitro Dissolution

The USP dissolution apparatus I with a 50 rpm basket rotational speed and an automated monitoring system (IBM Computer PK8620 series and PU 9605/60 tablet dissolution system software, Philips UGU, Vis NIR single beam spectrophotometer PU 8605/50 eight cell program, Epson LX850 printer and Watson-Marlow peristaltic pump) were used. For each sample point three tablets

were tested. The dissolution media were chosen according to the monograph of each drug in the USP.

The dissoluted drugs were analyzed by recording the absorbance at the corresponding λ_{max} of each drug (277 nm for salbutamol-SO4, 265 nm for meclizone HCl and 277 nm for theophylline and aminophylline). Using the automated monitoring system, the percentage of drug dissoluted was plotted against time.

Thermal Analysis

Powder samples of egg albumin, pure drugs and crushed tablets, accurately weighed (2 mg), were subjected to differential scanning calorimetry analysis with a scanning rate of 10°C/min (Perkin-Elmer DSC-4, USA).

RESULTS AND DISCUSSION

Table 1 shows the % compressibility and flowability of powder blends of the drug under study and egg albumin at different drug:egg albumin ratios,that were subsequently used for the preparation of direct compressed tablets. The drug egg albumin mixtures gave % compressibilities ranging between 12.4-32.5%. The flowability of these powder blends was ranked according to Jones T.M's tables of compressibility and flowability for pharmaceutical excipients (6) and came to be excellent, good, passable, or poor, where poor flowability is always accompanied with high compressibility. Drug free egg albumin showed 36.43 % compressibility and could be considered as acceptable direct compressed tablets filler where, excipients of compressibility upto 41% are used for direct compression of tablets (1).

The crushing strength of the prepared tablets is shown in Table 1. Although the same compression force was used for each drug at different drug:egg albumin ratio, the crushing strength was 7.93-14.47, 7.1-8.79, 3.47-7.96 and 3.56-8.49 kp for salbutamol-SO_4, meclizine-HCl, theophylline and aminophylline respectively, indicating that an increase in albumin content is accompanied by an increase of tablet crushing strength and generally, these tablets can withstand shocks occurring during handling, shipping and dispensing.

No disintegration was noticed for all the formulated tablets at the different drug:egg albumin ratios, although the disintegration test was applied for 2 hours in simulated gastric fluid.

Egg albumin tablets containing drugs of different physico-chemical properties were subjected to dissolution study. The tablets swell gradually and retain their geometry throughout the dissolution study for seven or eight hours. Figure 1 shows the release profile of the different drugs from direct compressed egg albumin tablets at different drug:egg albumin ratios. It was clear that the increase in albumin ratio caused significant retardation in release of salbutamol-SO^4, theophylline and aminophylline, while a change in albumin ratio did not alter the release properties of meclizine hydrochloride. According to the above observations, egg albumin in the direct compressed tablets behaved like swellable matrices that were proven to exhibit anomalous release kinetics (8) and could be considered as a suitable form for release control in oral drug administration and to modulate the release rate.

TABLE 1

Compressibility and Flowability of Drug-egg Albumin Powder Blends and Hardness of Direct Compressed Tablets Prepared at Different Drug:egg Albumin Ratios.

Drug	Drug:Albumin	% Compressibility	Flowability	Crushing Strength (kp)
Salbutamol-SO_4	2:1	12.4	Excellent	7.9 ± 0.33
	1:1	16.6	Good	8.9 ± 0.37
	1:2	24.2	Poor	10.0 ± 0.49
	1:4	30.0	Poor	14.4 ± 0.47
Meclizine-HCl	2:1	21.0	Passable	7.1 ± 0.20
	1:1	21.2	Passable	7.4 ± 0.28
	1:2	19.6	Passable	8.1 ± 0.37
	1:4	22.2	Poor	8.7 ± 0.29
Theophylline	2:1	29.1	Poor	3.4 ± 0.17
	1:1	26.7	Poor	3.7 ± 0.16
	1:2	24.0	Poor	5.0 ± 0.21
	1:4	22.3	Poor	7.9 ± 0.27
Aminophylline	2:1	31.6	Poor	3.5 ± 0.16
	1:1	32.2	Poor	3.9 ± 0.18
	1:2	29.5	Poor	5.3 ± 0.29
	1:4	32.8	Poor	8.4 ± 0.36

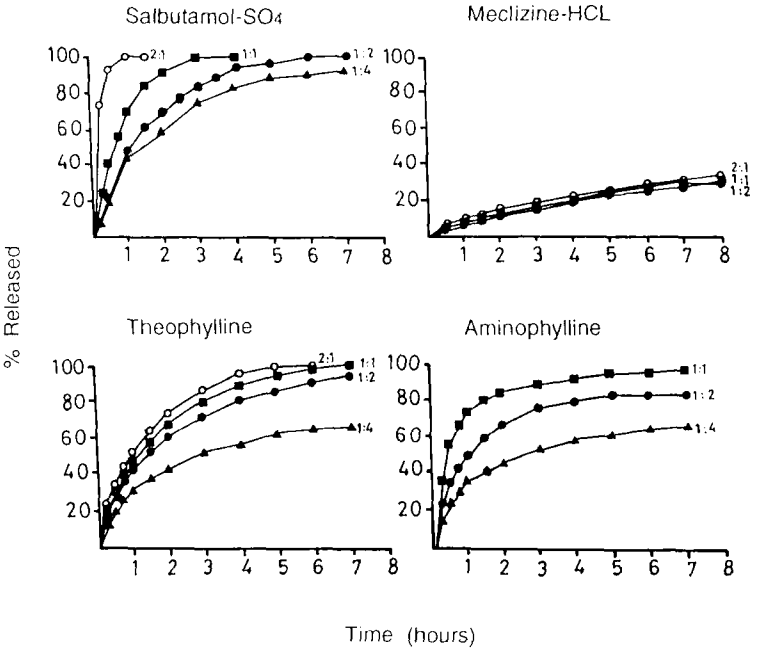

FIGURE 1

Dissolution profile of salbutamol-SO_4, meclizine-HCl, theophylline and aminophylline from direct compressed tablets prepared with different drug:egg albumin ratios at 37°C.

TABLE 2

Regression Coefficients for Release of Drugs from Egg Albumin Tablets at Different Drug:egg Albumin Ratios According to Zero-order, First-order and Diffusion Models and n Values.

Drug	Drug:albumin	Zero-order	First-order	Diffusion	n
Salbutamol-SO_4	2:1	0.992	0.996	0.998	0.360
	1:1	0.923	0.973	0.999	0.684
	1:2	0.918	0.93	0.986	0.720
	1:4	0.910	0.970	0.995	0.657
Meclizine-HCl	2:1	0.985	0.992	0.999	0.595
	1:1	0.991	0.992	0.993	0.670
	1:2	0.989	0.995	0.999	0.773
Theophylline	2:1	0.948	0.963	0.989	0.498
	1:1	0.949	0.970	0.989	0.508
	1:2	0.959	0.994	0.997	0.501
	1:4	0.940	0.961	0.985	0.480
Aminophylline	1:1	0.839	0.973	0.917	0.300
	1:2	0.911	0.968	0.970	0.400
	1:4	0.943	0.973	0.985	0.446

Release retardation was clear with the basic drugs salbutamol and meclizine, as well as with the acidic drugs theophylline and aminophylline and increased significantly with albumin matrix density in most cases.

The release kinetics of the selected drugs from the formulated tablets at different drug:egg albumin ratios were tested for zero, first and square root of time (diffusion controlled) mechanisms. The model with the higher correlation coefficient was judged to be the more appropriate model for the dissolution data. From Table 2, it is apparent that the release model of drugs for different tablet batches was not obeying zero-order kinetics, while both square root of time and first order release plots were nearly linear as indicated by the regression coefficients.

In order to further verify the release model the kinetics of drug release was evaluated by using the well-known exponential release equation,

$$\text{Fraction released} = kt^n$$

where t is time, k and n are constants, in which the exponent n indicates the kinetics of release (9). The n values were calculated for drug release profile at different drug:egg albumin ratios and the obtained values are shown in Table 2. In most cases the calculated n values showed anomalous release kinetics.

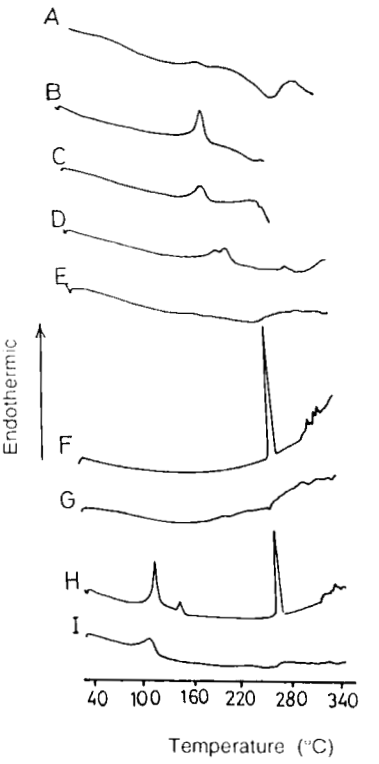

FIGURE 2

DSC thermograms of drug-egg albumin systems.

A. egg albumin. B. salbutamol-SO_4. C. tablet of salbutamol-So_4 with egg albumin(1:1). D. meclizine-HCl. E. tablet of meclizine-HCl with egg albumin (1:1). F. theophylline. G. tablet of theophylline with egg albumin (1:1). H. aminophylline. I. tablet of aminophylline with egg albumin (1:1).

In order to elucidate the release mechanism of drugs from egg albumin compressed tablets the interaction of drug with egg albumin was studied after tablet compression. The interaction was examined by DSC. Figure 2 shows the DSC thermograms of crushed tablets containing drug and egg albumin in a ratio of 1:1 compared with that of a powder mixture of pure drug and egg albumin. Each drug showed an endothermic peak corresponding to its melting point, while egg albumin showed a broad endothermic peak at about 70° and a broad exothermic peak at 297°C.

It was clear that after tabletting, the endothermic peaks of meclizine HCl (weak base), theophylline and aminophylline (weak acids) disappeared indicating an interaction of egg albumin with these drugs under the condition of direct

compression. On the other hand salbutamol, being a weak base was characterized with the existance of its peak after tabletting indicating no interaction with egg albumin at the applied conditions.

The above results could indicate that egg albumin binding may occur with both weak acid and weak base drugs which is in agreement with other findings for binding of drugs to plasma albumin (2, 10).

It appears that the release of salbutamol, that does not interact with egg albumin, could be controlled by just changing the drug albumin ratio in the formulated tablets while, drugs that show definite interaction with egg albumin, as was verified by DSC can give different release profile. Meclizine-HCl release rate was not changing even at different drug:egg albumin ratios and this could be because the rate determining step for drug release is the dissociation of the drug albumin complex or the solubility of the drug where, both are not depending on the density of the matrix. On the other hand if the rate determining step of drug release is the diffusion through the egg albumin matrix, then the increase of albumin matrix density can lead to more retardation for drug release and this may explain the release profile of theophylline and aminophylline. Because aminophylline is much more water soluble ($2.0\ 10^{-1}$ gm/ml) than theophylline ($8.3\ 10^{-3}$ gm/ml), its release profile could be only controlled by changing albumin matrix density where, drug dissolution is not having any effect on release.

In conclusion, in direct compression tablets, egg albumin can be used as a filler to control drug release. The release profile from the formulated tablets depends on the property of the drug. The release is controlled by drug interaction with egg albumin, drug diffusion through the egg albumin matrix or both.

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