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Influence of surfactant-treated starch on the disintegration and dissolution of sulphadiazine tablets

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The effects of treating cassava starch with sodium lauryl sulphate and Polysorbate 80 and the method of incorporating the treated and plain starch as disintegrant on the physical properties of sulphadiazine tablets were investigated. Disintegration and dissolution rates were faster with starch in which surfactant was incorporated in dry state than with starch treated with solution of surfactant. A direct correlation was observed between the Hardness–Friability Index and T90 values. Polysorbate 80-treated starch exhibited a better dissolution profile than SLS-treated starch.

We have been examining effects of treating cassava starch with sodium lauryl sulphate or polysorbate 80 by two different methods and also the effects of the method of incorporation of the treated and plain starch on the physical properties of sulphadiazine tablets.

Materials and method

Sulphadiazine BP, sodium lauryl sulphate (SLS), polysorbate 80 and magnesium stearate were from BDH Ltd (UK). Cassava starch was prepared in the laboratory from tubers of *Mannihot utilissima*.

Starch was treated with the surfactants in two ways: (a) starch was added to a 0·5% aqueous solution of the surfactant, stirred for about 6 h, filtered, dried at 50 °C, sifted and analysed for surfactant content, (b) a calculated quantity of the surfactant was mixed intimately with the starch and was analysed for surfactant content uniformity. Concentrations of SLS and polysorbate 80 in the final granulation were about 0·2%.

Granules were prepared by wet massing and screening using 10% w/w cassava starch mucilage as the binder and a sieve of mesh 1·7 mm. The quantity of plain or treated starch used as disintegrant was 5% of the drug. In some formulations, the whole amount was used as intragranular disintegrant while in other formulations half was used as intragranular and the other half as extragranular disintegrant. The granules were dried at 50 °C to a residual moisture content of about 1% and then dry-screened using the sieve of mesh 1·7 mm super-imposed on a 0·25 mm sieve. Granules retained by sieve 0·25 mm were used for compression. In those formulations where half of the starch was incorporated before wet massing, the remaining half was mixed with the dry-screened granules. 1% magnesium stearate was used as lubricant for all the batches.

Granules were compressed to tablets using an 11 mm diameter die-punch at a pre-set compression pressure keeping the volume of the die fill constant for all the batches. Tablets were tested for hardness, friability, disintegration time and dissolution rate. The dissolution medium used was 0·1 M HCl of pH 1·2.

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Results and discussion

The results are in Table 1. By keeping the moisture content at approximately the same level, it was assumed that its effect on the physical properties of tablets would be the same. It was also assumed that the 1% of lubricant would impart the same hydrophobic effect to all batches of granules. Thus the observed effects were expected to be due to the technique of treating the starch with surfactant and the method of incorporation of the treated or plain starch as disintegrant.

The disintegration time of tablets prepared using surfactant-treated starch was shorter than that of tablets

Table 1. Effect of surfactant-treated cassava starch on hardness, friability disintegration time (DT), T50 and T90 of sulphadiazine tablets. * See text. IG = Intra-granular; EG = Extra-granular; P = polysorbate.

Disintegrant	SA method*	Hardness (kg)	Friability (%)	H.F Index (%)	DT (min)	T50 (min)	T90 (min)
IG plain starch	—	5·46 ± 0·11	0·92	—	30·0	24	>90
IG & EG plain starch	—	5·30 ± 0·09	1·00	—	23·3	20	>90
IG SLS treated starch	a	4·86 ± 0·10	1·42	57·67	14·3	17	50
IG & EG SLS treated starch	a	4·88 ± 0·14	1·64	56·14	13·2	16	43
IG P 80 treated starch	a	4·80 ± 0·08	1·55	52·22	16·2	15	37
IG & EG P 80 treated starch	a	4·48 ± 0·09	1·72	49·05	15·4	12	32
IG SLS treated starch	b	4·20 ± 0·10	1·50	47·21	2·4	9	30
IG & EG SLS treated starch	b	4·30 ± 0·08	1·85	43·77	2·2	9	28
IG P 80 treated starch	b	3·75 ± 0·09	1·70	37·27	2·0	7	25
IG & EG P 80 treated starch	b	3·80 ± 0·07	2·10	34·15	1·8	7	20

prepared using plain starch. Starch in which the surfactant was incorporated in the dry state proved to be a more effective disintegrant (disintegration time 2 min) than the starch treated with solution of surfactant (disintegration time 13–16 min).

All batches of tablets formulated with surfactant-treated starch gave higher dissolution rates than those formulated with plain starch. Both T50 and T90 values of tablets prepared using plain starch were much higher than those prepared using the treated starch. Release rates of drug from tablets prepared using plain starch were also much lower; 90% of drug was not released even after 90 min. Polysorbate 80-treated starch gave better dissolution rate profiles than SLS treated starch.

Generally, tablets containing both intra- and extragranular starch disintegrated faster and released the drug more rapidly than those containing only intragranular starch. For all the batches of tablets formulated, a direct correlation was observed between the Hardness-Friability Index (HFI) and the T90 values; the higher the HFI, greater the time required for 90% of the drug to go into solution. The method of Mendes & Brannon (1968) was used to calculate the HFI values. It was also observed that tablets containing intragranular surfactant-treated starch gave higher values of HFI and T90 than those where starch was used as both intra- and extragranular disintegrants. Also SLS-treated starch gave higher values of both HFI and T90 than those where Polysorbate 80-treated starch was used.

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Metronidazole-induced myocardial depression: chemical and pharmacological studies on the role of calcium in-vitro

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The interaction of metronidazole with calcium to form a water-soluble complex has been studied by titration with ethylenediaminetetraacetate (EDTA), direct current and pulse polarographic reduction steps of the nitro-group at pH 5 and 7, and by ultraviolet absorption. Stoichiometric calculations, X-ray powder diffraction pattern of the synthesized metronidazole-calcium complex, and molecular ion peak at *m/z* 381 in the mass spectrum of this product, showed that a 2:1 complex is formed. The interaction of metronidazole with calcium on myocardial contractile performance of guinea-pig electrically-driven isolated left atria in physiological solution was also examined. Metronidazole induced a sustained, concentration-dependent depression of the tension that was reversed by changing the bathing fluid to physiological solution, and/or by adding excess calcium ion. The drug-induced negative inotropic response was antagonized competitively by increasing calcium ion in the bath, whereas noradrenaline antagonized metronidazole-induced negative inotropic responses non-competitively. Addition of the metronidazole-calcium complex to the bath did not affect normal myocardial contractile performance. The results show that metronidazole produces a direct negative inotropic effect on isolated atrial muscles by interfering with Ca^{2+}, and by preventing Ca^{2+} function in the events leading to contractile activity of atrial muscles.

Metronidazole is commonly prescribed for the treatment of trichomoniasis, amoebiasis and anaerobic infections in doses as high as 4 g daily. The troublesome side-effects associated with heavy medication include myocardial depression (Balsara et al 1975) and Quinke's oedema (Sheveliakov 1978).

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In the heart muscle, excitation-contraction coupling is believed to depend upon a superficial membrane source of calcium ion (Ca^{2+}) (Shine et al 1971; Langer 1973). Balsara et al (1975) have indicated that metronidazole induces negative inotropic responses in isolated cardiac muscle preparations. Thus, the myocardial depressant effect could be taken to imply interference of the drug with excitation-contraction coupling processes in the heart muscle.

We have recently shown that, under certain conditions, metronidazole interacts chemically with some divalent and trivalent metal cations, such as Ca^{2+}, Zn^{2+} and Ti^{3+}, to form water-soluble complexes (Essien & Femi-Onadeko 1981). Metronidazole could, therefore, be acting as a sequestering agent. Our pharmacological studies have also shown that the drug alters calcium ion-dependent processes in experimental animals while exogenous administration of Ca^{2+} quickly reverses the cumulative neuromuscular blocking effect, probably by displacing accumulated metronidazole from Ca^{2+} – receptor binding sites at the axonal membrane. Thus, the drug would be acting in a manner essentially similar to that established for aminoglycoside antibiotics by Adams & Mathew (1974), or the reversal effect could be due to replacement of Ca^{2+} ions depleted from the myomembrane by metronidazole interference. Therefore, metronidazole could be acting by disrupting the participation of the superficial Ca^{2+} membrane pool believed to represent a source of contractile Ca^{2+} in the coupling of membrane events with mechanical activity (Goodman & Weiss 1971b).