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THE PHARMACEUTICAL DEVELOPMENT AND BIOAVAILABILITY OF CIMETIDINE CAPSULE AND TABLET FORMULATIONS

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ABSTRACT

The development of a suitable oral solid dosage form of cimetidine has been examined from the standpoint of equal bioavailability for different formulations. The in vitro characteristics of one capsule and four tablet formulations were determined. From the areas under the blood level/time curves in healthy volunteers, equal bioavailability was shown between the capsule, the original tablet formulation chosen for early clinical trials and the final tablet formulation used for commercial production.

INTRODUCTION

The transfer of a tablet formulation from a low output single punch tablet machine to a rotary machine such as the Manesty B3B, and then to a high speed tablet machine such as the Manesty Express 25, can involve a lengthy development programme, which may require modifications to be made to the original tablet formula. Where high dose compounds are involved, in which more than 50% of the tablet weight is active drug, the compression characteristics of the compound become very important. Cimetidine, an orally active H_2-receptor antagonist (1), is one such compound.

During the early stages of the pharmaceutical development of a new drug, the drug substance is often in short supply and for this reason the first oral dosage form has to be produced from the least possible amount of drug. The simplest method is to loosely fill a powder mixture of the drug and any necessary excipients into hard shell gelatin capsules. With the correct selection of excipients dissolution will normally be rapid and complete from such a formulation (2) and it can therefore be used as a baseline for further bioequivalence studies on tablet formulations as they are developed. This approach was used for cimetidine.

Thus the early clinical trials were carried out using a capsule formulation, whilst tablet development proceeded as more drug substance became available.

This paper outlines the formulation development necessary to scale up the tableting of cimetidine to high volume production and the bioavailability studies which were conducted on various formulations in order to confirm the final tablet formulation.

MATERIALS

In vitro and *in vivo* studies were conducted on one capsule and three tablet formulations during the development of cimetidine tablets. All the excipients used were of B.P., B.P.C. or E.P. quality except where novel or non-compendial materials were used in which case appropriate in-house specifications were drawn up.

Capsule Formulation:	Lactose based dry powder mix containing 50% cimetidine.
Tablet Formula A:	Lactose/maize starch based granulation with additional maize starch as an extragranular disintegrant, containing 77% cimetidine.
Tablet Formula B:	Microcrystalline cellulose based granulation with maize starch as an extragranular disintegrant, containing 72% cimetidine.
Tablet Formula C:	Microcrystalline cellulose based granulation with maize starch and sodium starch glycollate as extragranular disintegrants, containing 72% cimetidine.

Tablets were prepared containing either 200 mg or 300 mg cimetidine. Identical granulations were used for the two strengths, the quantity of drug per tablet being determined by means of tablet weight. All the tablets were film coated by standard techniques using an organic solvent based polymer solution.

METHODS

In Vitro Test Methods for Capsules and Tablets: Potency was determined on a sample of 20 tablets/capsules. They were finely powdered and a sample equivalent to about 100 mg cimetidine shaken with 200 ml 0.1 N sulphuric acid. The sample was filtered and diluted 40 times with more acid and the absorption read at 218 and 260 nanometers, the difference between the two readings being used to calculate the potency, knowing the E_1^1 for cimetidine for the particular u.v. spectrophotometer used. The mean hardness of the tablets was measured on a sample of 20 using a Heberlein Tester, which determined the diametral crushing strength of the compacts. The mean disintegration time was determined in water at 37°C by the method of the B.P. (3) on two samples of five tablets/capsules. The dissolution rate was determined in water at 37°C by the Rotating Basket method of the U.S.P. (4) using a stirring speed of 100 r.p.m.

TABLE 1: Physical Characteristics of the Cimetidine Oral Dosage Forms used in the Bioavailability Studies

Dosage Form		Weight mg	Hardness kg	Disintegration Time Minutes	Dissolution Rate. % Cimetidine in solution after 15 Minutes	30 Minutes	60
Capsule	200 mg	404	-	2½	92	97	-
Tablet Formula A	200 mg	271	11.3	6	99	99	-
Tablet Formula A	300 mg	397	10.8	6½	97	99	99
Tablet Formula B	300 mg	435	21.6	13¼	58	85	99
Tablet Formula C	200 mg	283	9.7	1¾	100	-	-

In-Vivo Tests in Volunteer Subjects: These were all conducted in accordance with the Declaration of Helsinki (5) in healthy human volunteers. Blood levels of cimetidine were determined by an extraction procedure followed by an H.P.L.C./U.V. assay.

Extraction Procedure: 2 ml of a whole blood sample were pipetted into a polypropylene centrifuge tube to which was added 1 ml of 1.0 M carbonate buffer at pH 9.0, containing a concentration of internal standard metiamide (1) of the same order as that to be expected in the sample. The sample was vortex mixed and 4 ml of *n*-octanol added before the tube was stoppered and revolved on a blood mixer for 15 minutes. After centrifuging 3.5 ml of the n-octanol layer was transferred to another centrifuge tube containing 3 ml of 0.02 N hydrochloric acid. Back extraction into the acid occurred when the sample was revolved for a further 15 minutes. The two layers were separated by centrifuging and the octanol layer discarded before 2.5 ml of the acid phase was transferred to a third centrifuge tube containing 250 μl of ethanol. After homogeneity had been achieved by vortex mixing, sufficient potassium carbonate (circa 5 g) was added to saturate the solution and 'salt-out' the ethanol. 200 μl (or as much as possible) of the ethanol layer was removed as a sample for H.P.L.C. It was stored at - 20°C if not required immediately for assay.

High Pressure Liquid Chromatography/Ultraviolet Detection: The conditions used for the estimation of the cimetidine content of the ethanol samples were as follows:

Column:	Lichrosorb SI 60 5 (250 mm x 3.5 mm i.d.)
Solvent System:	200 Acetonitrile: 20 Methanol: 6 Water: 1.5 NH_4OH (S.G. 0.88)
Flow Rate:	1.5 ml/minute (Pressure 2000-3000 p.s.i.)
Retention Time:	Cimetidine - approximately 4 minutes Metiamide - approximately 3 minutes
Detection:	Perkin Elmer LC55 U.V. Spectrophotometer set at 228 nm and giving full scale deflection for Δ abs of 0.015 units)

A saline or pre-dose blood sample to which known amounts of both cimetidine and internal standard had been added was also taken through the complete procedure. The ratio of cimetidine to standard was calculated for both the known and unknown concentrations of cimetidine using either the peak heights or areas under the peaks, and, since the internal standard was common to both samples, the concentration of cimetidine in the unknown sample could be determined. The principle of this analytical technique has been given by Randolph et al (6), but the method used in this laboratory was considerably modified in scale and in some of the steps of the extraction procedure.

RESULTS AND DISCUSSION

The comparison of cimetidine blood concentrations at frequent intervals after oral administration was made for various tablet formulations and for cimetidine given in hard shell gelatin capsules. The *in vitro* characteristics of the various formulations relevant to the bioavailability studies are shown in Table 1.

In the first kinetic study (Table 2) the areas under the blood concentration vs time curves for 200 mg Formula A tablets were compared with those obtained after the administration of cimetidine in gelatin capsules in a 6 hour study. This was carried out to confirm that the results from the clinical trials would not be biased by different drug release rates from the oral dosage form used.

The areas for the first 6 hours after dosing were very similar for the tablet and capsule, both as regards the mean area and the variation within the group of 4 subjects. (A paired 't' test gave the value for P as > 90% in this study). The *in vitro* examination of these two formulations showed that the cimetidine was released rapidly into solution from both the capsule and the tablet (Table 1) and no differences were expected or found *in vivo*.

However, on scaling up this process from a batch size of 100,000 tablets on a Manesty B3B Rotary Tablet machine to larger batches, which were to be compressed on the high speed Manesty Express 25 tablet press, problems of severe tablet lamination and capping occurred. Transfer of the process to Stokes Compression equipment gave the same unsatisfactory results, even with low output machines operating at low speed. No alteration of the granulation process or compression conditions could overcome the problem and formulation development was necessary. The result was Formula B, which gave tablets with excellent

TABLE 2: Areas under the Blood Concentration vs Time Curves for Subjects Receiving 200 mg Cimetidine in a 6 Hour Study.

Subject	Area under blood concentration vs time curve mg $l^{-1}min^{-1}$	
	Formula A Tablet	Capsule
R.Y.	239	180
D.O.	150	171
B.B.	229	262
D.R.	178	172
Mean ± S.D.	199 ± 42	196 ± 44

compression properties and low friability, and hence ideally suited to film coating. Using a dose of 300 mg in 3 human subjects, Formula B was compared with Formula A in a bioavailability study. The areas under the blood concentration vs time curves for this study are shown in Table 3.

The average area (367 mg $l^{-1}min^{-1}$) for a 300 mg Formula A tablet was 57 mg $l^{-1}min^{-1}$ greater than that for a 300 mg Formula B tablet, and this increase was observed in all three subjects. Consequently, a paired 't' test comparison of these means indicated a significant difference ($P < 1\%$) for the two tablet formulations.

This result was presaged by the available *in vitro* data (Table 1) which showed that the Formula B tablet, which had been compressed to a greater hardness, took longer to dissolve. An investigation of the compression properties of Formula B (Figure 1) revealed that the *in vitro* characteristics of tablets prepared to this formulation were greatly influenced by the force used to compress the tablet. In commercial production control of the compression force on a tablet machine during a run is still largely empirical although automatic controlling techniques are now available and in operation in some plants. Without these controls, fluctuations in compression force can occur during the course of a single batch. In the present case it was known that the formulation would be required to be used in several different manufacturing plants and it was therefore decided not to proceed with a tablet formulation which was susceptible to large changes in disintegration time for small changes in compression force.

This relationship is illustrated in Figure 1 where in the absence of an instrumented tablet press, the ratio of the tablet weight (mg) to the tablet thickness (mm) is used as an indication of compression force ("Compression Ratio",

TABLE 3: Areas under the Blood Concentration vs Time Curves for Subjects Receiving 300 mg Cimetidine in a 6 Hour Study.

Subject	Area under blood concentration vs time curve mg $l^{-1}min^{-1}$	
	Tablet Formula A	Tablet Formula B
P.F.	363	311
C.S.	335	283
G.T.	402	335
Mean ± S.D.	367 ± 34	310 ± 26

FIGURE 1

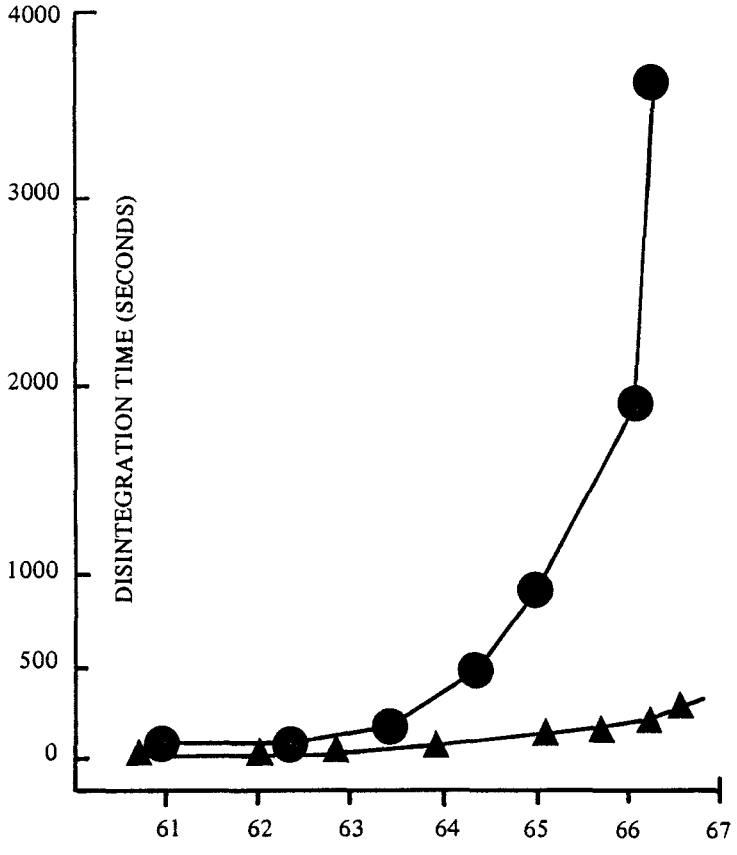

FIGURE 1

The Effect of Increasing Compression on the Disintegration Time of 200mg Uncoated Core Tablets of Formula B ● and Formula C ▲

Berry and Rideout, (7). For these investigations uncoated core tablets were used in order to simplify the task and to eliminate film coating as a source of batch to batch variation in the tablets. Formula B tablets showed a very steep rise in disintegration time with increasing force of compression, the rise starting at a compression ratio of about 64, equivalent in this instance to a tablet crushing strength of about 11 kg.

Various modifications to Formula B were investigated and Formula C was the result. The *in vitro* comparison of the two formulations shown in Figure 1 revealed that Formula C did not show the rapid increase in disintegration time with increasing force of compression that occurred with Formula B, even when compressed to a crushing strength of about 18 kg.

For 200 mg cimetidine tablets a crushing strength of at least 8 kg is required for the tablet core so that it can be successfully film coated. In order to achieve these crushing strengths it was more appropriate to use Formula C since tablets of this formulation are unlikely to have high disintegration times if over compressed during manufacture. Two bioequivalence studies indicated that Formula C gave areas under blood concentration vs time curves for cimetidine that were indistinguishable statistically from those produced by the capsule formulation. However, it should be noted that differences in the mean values of some 30% would be required to demonstrate a significant difference by the paired 't' test method.

The results of these two studies are given in Tables 4 and 5, and show that a 6 hour study or a 3½ hour study could be used to demonstrate bioequivalence; using Formula C the area at 210 minutes in the 6 hour study (146 ± 47 mg $l^{-1}min^{-1}$) was very similar to the total area (140 ± 51 mg $l^{-1}min^{-1}$) for the study which was only continued for 210 minutes after tablet administration. Similarly for the capsule study, the respective figures were 144 ± 38 and 151 ± 37 mg $l^{-1}min^{-1}$.

Statistical analyses on all the data, using 't' tests or paired 't' tests as appropriate, indicated that there was no demonstrable difference in bioavailability between capsule formulated cimetidine, or cimetidine in Tablet Formulations A and C. For Tablet Formulation B there was not bioequivalence, the availability being reduced to about 85% of the Formula A bioavailability, this difference being statistically significant at the 1% level, and observed in all the individual comparisons (Table 3).

The data presented here have indicated that it is possible to make tablet formulations of cimetidine which have a bioavailability equivalent to that of encapsulated material, when given by the oral route.

In relation to an intravenous dose, for which the bioavailability is defined as 100%, the presentation of cimetidine by the oral route results in a bioavailability of about 70% (8). This percentage applies to oral doses of cimetidine up to 400 mg in human subjects, as judged by the area under the blood concentration vs time curve for different oral doses (8,9). The areas found for 200 and 300 mg doses in the present study confirm this proportionality between dose and bioavailability.

One batch of tablets (Formula B, 300 mg) gave a lower average bioavailability of cimetidine than the first formulation tested. Formula B was

TABLE 4: Areas under Blood Concentration vs Time Curves for Subjects Receiving 200 mg of Cimetidine in a 6 Hour Study.

Subject	Areas under blood concentration vs time curves mg $l^{-1}min^{-1}$			
	Tablet Formula C		Capsule	
	Area @ 360 mins	Area @ 210 mins	Area @ 360 mins	Area @ 210 mins
R.B.	193	143	193	128
W.B.	241	142	231	167
R.G.	247	169	314	196
J.M.	95	72	131	96
M.M.	367	216	234	162
P.S.	194	133	164	112
Mean ± S.D.	223± 89	146 ± 47	211± 64	144± 38

TABLE 5: Areas under the Blood Concentration vs Time Curves for Subjects Receiving 200 mg of Cimetidine in a 3½ Hour Study.

Subject	Areas @ 210 mins under blood concentration vs time curves mg $l^{-1}min^{-1}$	
	Tablet Formula C	Capsule
R.L.	139	182
B.J.	214	170
M.B.	156	134
C.H.	78	104
M.C.	207	173
P.C.	118	116
R.H.	123	204
F.M.	82	123
Mean ± S.D.	140± 51	151 ± 37

developed specifically to overcome the mechanical problems which occurred during compression and film coating with Formula A on a large scale.

Consequently the lower bioavailability demonstrated here may well have been the result of incomplete disintegration or dissolution *in vivo* and hence a reduction in

the amount of cimetidine available in those areas of the upper gastrointestinal tract where the most rapid absorption takes place.

The final product (Formula C) was a combination of the better *in vitro* and *in vivo* features of the previous formulations, giving a stable, readily manufactured tablet with bioavailability equivalent to that of the capsule formulation.

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REFERENCES

1. R.W. Brimblecombe, W.A.M. Duncan, G.J. Durant, J.C. Emmett, C.R. Ganellin and M.E. Parsons, J. Int. Med. Res., 3, 86 (1975)
2. J.M. Newton, Pharm. Weekblad, 107, 485 (1972)
3. British Pharmacopoeia, Her Majesty's Stationery Office, London, 1973, Appendix XIXA p. A131
4. United States Pharmacopoeia, The USP Convention, Inc., 1975, p. 651
5. Declaration of Helsinki, Adopted by 18th World Medical Assembly, Helsinki, Finland, World Med. J., 11 (5), 281 (1964)
6. W.C. Randolph, V.L. Osborne, S.S. Walkenstein and A.P. Intoccia, J. Pharm. Sci. 66 (8), 1148 (1977)
7. H. Berry and C.W. Ridout, J. Pharm. Pharmacol., 2, 619 (1950)
8. R. Griffiths, R.M. Lee and D.C. Taylor, in "Excerpta Medica. Proceedings of the Second International Symposium on Histamine H_2-Receptor Antagonists", W.L. Burland and M.A. Simkins, eds., Oxford, 1977, p. 38
9. R.M. Henn, J.I. Isenberg, V. Maxwell and R.A.L. Studevant, New Engl. J. Med. 293, 371 (1975)