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EFFECTS OF BINDERS AND MOISTURE CONTENT ON THE DISINTEGRATION, HARDNESS AND FRIABILITY OF PARACETAMOL AND ORPHENADRINE CITRATE TABLETS

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ABSTRACT

The effects of binders and moisture content on the disintegration time, friability and hardness of paracetamol and orphenadrine citrate tablets at different storage conditions were investigated. These parameters were determined after one, four and sixteen weeks of storage .

The use of starch, ethocel or CMC Na as binders gave unsatisfactory tablets because of their high

friability. Unacceptably high disintegration times were obtained, particularly at higher storage temperatures when PVP was used. Capping and yellow spotting observed in gelatin formulations makes this binder unsuitable for use. Methocel granulations yielded satisfactory tablets with acceptable disintegration time , hardness and friability and were unaffected by storage at different conditions of temperature and humidity.

INTRODUCTION

Paracetamol is generally administered as tablets containing 500 mg of active drug formulated with the appropriate amounts of other excipients in order to confer desirable properties on the granules and on the final product. Factors affecting the properties and compression of paracetamol tablets are numerous and the formulation and evaluation of such tablets have been the subject of several studies (1-3). The type and amount of excipients used in the formulation and the method of incorporating them have often been shown to influence such tablet properties as their mechanical strength, friability, disintegration and dissolution times (4,5). The addition of Avicel in relatively large amounts (20-30%) to paracetamol has been shown by many workers (6,7) to reduce the incidence of capping and

lamination. Furthermore, the amount of Avicel added was found to bear a direct relationship with the plasto-elasticity of the mixtures and the tensile strengths of their tablets (8,9). In general, the greater the amount of Avicel in a mixture, the higher its plastic compression and the lower its elastic recovery. Therefore, the modification of plastic and elastic characteristics of paracetamol is necessary for the compression of satisfactory tablets that do not show capping or lamination (10,11).

The physical properties of compressed tablets are also greatly influenced by the moisture content of powder mixture. Bangudu and Pilpel (12) have shown that the addition of between 2-4% of water to paracetamol-cellulose mixtures increased the tensile strength of tablets. Also, Chowhan (13) investigated the moisture-induced hardness increase and the interrelationships among moisture, hardness, disintegration and dissolution in compressed tablets. His results suggested that moisture gain and subsequent loss on storage could account for major increases in hardness. Other workers have also studied the effects of moisture content on physical parameters, such as, hardness and disintegration (14,15), friability (15,16), compression properties (17), and flowability of granules (18).

The relative importance of various formulation and process variables and their interactions in model paracetamol tablets were evaluated by Sanderson et al.(19) using a factorial design method. These workers established that the mixing time was a more significant factor in affecting the tensile fracture stress of the tablets than the particle size, amount of starch added or the compaction pressure.

The possibilities of changes in tablet characteristics during their shelf life must also be considered in formulation studies. The effect of storage on tablet properties essentially depends on the formula whatever the manufacturing method is. Adverse effects on tablet hardness were reported as a result of tablet ageing in conditions of high humidity (20,21).

It was noticed in our laboratories that the inclusion of orphenadrine citrate to paracetamol in tablet formulations significantly altered the physical properties of these tablets. The purpose of this study was therefore to investigate some of the factors affecting the tabletting of paracetamol in combination with orphenadrine citrate.

MATERIALS

All materials were used as received from the manufacturer or distributor with no further purification.

Paracetamol complied with requirements of the British Pharmacopoeia and was purchased from Hoechst (Frankfurt, West Germany); Orphenadrine Citrate (Taurus, Geneva, Switzerland); Avicel PH-101(FMC, Philadelphia, PA, USA); Aerosil 200 (Degussa, Frankfurt, West Germany); Primojel (Agena International, Vienna, Austria); corn starch (Foster Clark Ltd., Malta); gelatin, Methocel E-50,Ethocel E-50 and magnesium stearate (E. Merck, Darmstadt, West Germany); polyvinylpyrrolidone (PVP) (Basf, Ludwigshafen, West Germany; sodium carboxymethyl cellulose (Biochemie, Kundl/Triol-Austria).

METHODS

Preparation of Granules: The granulations containing paracetamol and orphenadrine citrate were prepared by the wet method according to the formula:

Paracetamol	75.00%
Orphenadrine Citrate	5.83%
Aerosil 200	0.50%
Magnesium Stearate	0.50%
Primojel	1.50%
Avicel PH-101 / Binder	16.67%

TRIAL	Binder	%-Binder	Avicel PH-101
A1	Starch	5.0	11.67
B1	PVP	5.0	11.67
C1	Methocel E-50	4.0	12.67
D1	Ethocel E-50	1.5	15.17
E1	Gelatin	3.0	13.67
F1	CMC Na	1.5	15.17

Moisture content of trials A1 to F1 was adjusted to around 1.0%. Trials A2 to F2 were prepared according to the corresponding formulae, but their moisture was adjusted to around 2.0%.

The method of preparation initially involved mixing of paracetamol and orphenadrine citrate powders in a cubic mixer for 30 minutes and then granulation with the appropriate binder in solution. The wet masses were passed through a 2.5 mm seive and dried in trays in an oven at 50^{o}C until the desired moisture level was reached. The dry granulations were screened through a 1.0 mm screen and mixed with the rest of the excipients for 10 minutes.

Compression: Tablets were compressed by means of a rotary machine (Manesty Model D3B) at a constant compression force. The punches and die were 12.7 mm in diameter and flat faced. The tablet weight was 600 mg.

Moisture Determination: The granulation moisture was determined by the USP loss on drying method and with a moisture balance (Mettler Model LP 15). The percent weight loss on drying was read directly from the balance. The conditions for the loss on drying method were 90°C for 5 hours. Based on the results of the two methods, the moisture balance method was used throughout this investigation.

Disintegration Time: The disintegration apparatus consisted of a basket-rack assembly and a 1-litre beaker as described in the USP (Erweka Model ZT3). The beaker containing 900 ml of distilled water was maintained at 37°C in a constant temperature water bath. The disintegration times of the indivisual tablets were noted, and the mean of six tablets was calculated.

Hardness Determination: An Erweka hardness tester (Model TBH 28) was used to determine the hardness of ten tablets and their range was recorded.

Friability Determination: Tablet friability was determined using an Erweka instrument (Model TAR). Ten tablets were rotated at 40 rpm for 10 minutes and the percentage weight loss was determined.

Storage: Tablets were stored at different conditions of temperature and humidity, viz., room temperature,

35°, 45° + 65% relative humidity and 55°C and were tested after one, 4 and 16 weeks of storage.

RESULTS AND DISCUSSION

The effectsof binders and moisture content on the disintegration time, hardness and friability of compressed tablets at different storage conditions are presented in Tables 1, 2 and 3, respectively. These parameters were determined at zero time and after one, four and sixteen weeks of storage.

Binders, by their capacity to aggregate powders, whether used dry or in solution, play a significant role in disintegration which they tend to slow down. This is a function of the viscosity of the microenvironment which forms around the tablet during disintegration (22).

Moisture is also an important factor to be considered in tablet formulation. Chowhan (23) investigated the role of binders in moisture induced hardness increase in compressed tablets and established that the magnitude of the hardness increase is related to the type and amount of binder used in wet granulation. However, the moisture-induced hardness increase had no effect on the tablet disintegration time and *in vitro*

TABLE (1)

Effect of Binders, Moisture and Storage Conditions on the Disintegration (min) of Paracetamol and Orphenadrine Citrate Tablets

Trial	Initial Value	Room Remp.			Temp. 35°			Temp. 45° + Rel. Humidity (65%)			Temp. 55°		
		Week			Week			Week			Week		
		1	4	16	1	4	16	1	4	16	1	4	16
A1	1	1	1	1	1	1	1	1	1	1	1	1	1
A2	1	1	1	1	1	1	1	1	1	1	1	1	1
B1	10	10	10	10	20	13	10	20	17	20	20	20	25
B2	7	7	10	11	13	15	9	16	17	14	17	17	18
C1	4	4	3	2	4	3	2	5	2	2	4	4	2
C2	4	2	3	2	3	3	2	3	2	2	3	3	2
D1	1	1	1	1	1	1	1	1	1	1	1	1	1
D2	1	1	1	1	1	1	1	1	1	1	1	1	1
E1	3	5	6	6	5	5	5	4	4	5	4	6	6
E2	3	6	8	13	8	8	8	8	9	17	10	10	11
F1	1	2	1	1	1	2	1	2	1	1	1	1	1
F2	1	1	1	1	1	1	1	1	1	1	1	1	1

TABLE (2)

Effect of Binders, Moisture and Storage Conditions on the Hardness (Kp) of Paracetamol and Orphenadrine Citrate Tablets

Trial	Initial Value	Room Temp.			Temp. 35°			Temp. 45° + Rel. Humidity (65%)			Temp. 55°		
		Week			Week			Week			Week		
		1	4	16	1	4	16	1	4	16	1	4	16
A1	5-7	7-10	8-10	9-14	8-10	8-10	7-10	10-13	10-14	13-15	10-13	10-13	13-15
A2	4-6	5-7	5-7	6-9	6-7	5-7	4-7	6-9	7-9	9-10	7-9	7-10	3-7
B1	12-17	13-15	14-18	12-19	14-18	15-17	12-17	18-22	18-22	32-34	15-21	24-26	17-32
B2	13-16	16-18	17-20	19-22	26-28	18-21	20-21	23-26	28-32	32-34	19-21	19-22	24-30
C1	13-16	13-16	14-17	16-19	15-17	15-17	16-20	14-16	14-18	18-20	16-17	13-15	13-17
C2	10-12	12-15	13-15	14-17	13-14	12-14	13-14	13-15	13-16	15-17	14-16	10-12	12-15
D1	6-8	8-9	7-8	6-10	7-10	8-10	7-10	6-9	8-9	8-9	7-9	5-8	7-9
D2	5-8	7-8	6-9	6-9	7-9	7-9	7-8	7-9	7-9	7-10	6-8	6-9	8-9
E1	8-12	11-14	10-12	11-13	12-13	12-13	11-15	12-14	10-13	15-17	10-14	10-14	10-13
E2	10-14	13-15	12-16	16-19	15-17	14-17	14-18	16-19	18-20	19-20	15-17	17-19	15-16
F1	7-10	9-11	8-10	8-10	8-10	8-10	8-10	9-11	9-11	10-12	7-9	8-10	7-9
F2	6-10	10-12	10-12	10-12	11-13	9-12	9-12	11-13	12-14	14-15	13-14	10-14	10-13

TABLE (3)

Effect of Binders, Moisture and Storage Conditions on the Friability (%) of Paracetamol and Orphenadrine Citrate Tablets

Trial	Initial Value	Room Temp.			Temp 35°			Temp.45° + Rel. Humidity (65)			Temp. 55°		
		Week			Week			Week			Week		
		1	4	16	1	4	16	1	4	16	1	4	16
A1	3.6	3.6	3.7	5.0	3.4	3.4	7.0	4.4	3.0	3.8	4.0	7.0	4.0
A2	8.0	7.0	8.0	10.0	7.0	9.0	12.0	7.0	6.5	7.6	6.0	4.0	12.0
B1	1.8	2.0	2.0	2.2	4.0	2.0	5.5	1.3	1.5	0.55	0.9	1.4	0.6
B2	0.5	0.5	0.4	0.8	0.5	0.3	0.6	0.5	0.2	0.4	0.4	0.4	0.4
C1	0.7	0.5	0.5	1.0	0.5	0.5	1.4	0.9	0.7	1.0	0.5	0.5	1.0
C2	0.5	0.7	0.8	1.5	0.9	0.9	1.3	0.8	0.6	1.0	0.8	0.9	1.0
D1	6.5	5.0	6.0	7.7	3.0	7.0	9.5	5.6	6.0	10.0	7.8	7.5	10.7
D2	4.0	4.7	6.0	7.0	5.0	7.0	8.0	4.5	6.0	6.0	5.0	5.0	6.0
E1	3.0	2.5	3.0	4.5	0.8	2.5	4.8	2.5	2.8	4.5	3.0	3.0	6.0
E2	1.3	1.1	1.5	1.7	2.5	1.5	1.3	0.8	1.0	1.1	1.0	2.0	1.2
F1	4.0	8.0	6.0	5.5	5.0	6.0	6.6	5.0	5.0	4.5	5.5	7.0	5.0
F2	5.0	3.5	3.5	3.3	6.0	3.5	3.9	3.5	3.0	2.9	3.3	3.0	3.4

drug dissolution. Furthermore, Chowhan and Palagyi(24) demonstrated the unusually important role of the moisture content of the granulation at the time of compression in the hardness increase phenomenon of compressed tablets. These workers found that tablets compressed from granulations with high moisture content increased in hardness after storage, whereas those compressed from low moisture granulations showed no increase in hardness on storage.

In this study, tablets compressed from PVP-granulations exhibited long disintegration times. However, the disintegration time was generally shorter in tablets obtained from higher moisture granulations. A noticeable increase in the disintegration time was observed when tablets were stored at higher temperatures. The effect of PVP on the variation in disintegration time of tablets during their storage was also investigated by Alam and Parrott (25). PVP was shown to have no effect on disintegration during storage. Although tablets having a higher moisture content showed a lower disintegration time, their hardness was slightly higher with a correspondingly lower friability. The reason behind this is not known but is probably related to easier wettability of the higher moisture containing tablets. The hardness of these tablets was also found to show an increase at higher storage temperatures. Fur-

thermore, yellowish discolouration in the form of spotting appeared on the surfaces of PVP-tablets having a higher moisture content which on longer storage spread tocover the whole of tablet surfaces. This phenomenon was more pronounced at higher storage temperatures. Tablets having a lower moisture content exhibited yellow spotting only after sixteen weeks of storage and at higher temperatures. These tablets also showed a slight tendency for capping and lamination.

When gelatin was used as a binder, an increase in the moisture content of the granulations gave slightly slower disintegrating tablets which was accompanied by an increase in hardness and a corresponding decrease in friability. The disintegration time was unaffected by storage conditions and this is in contradiction with the results obtained by Nakabayashi et al. (26) where changes in disintegration of gelatin tablets on storage were observed. Gelatin tablets formulated with a higher moisture content showed a slightly greater hardness and a marginally lower friability when stored at higher temperature and humidity conditions. After sixteen weeks of storage, formulations containing lower moisture showed a noticeable increase in friability at all storage conditions. However, both gelatin formulations were considered to be unsuitable since they exhibited a ready tendency for capping. Also, storage of these

tablets at 45° or 55°C resulted in a slight yellowish discolouration which was more noticeable after sixteen weeks.

Tablets formulated with sodium CMC having either 1.0% or 2.0% moisture gave fast disintegrating tablets, however, those obtained from granulations containing a higher moisture level were slightly harder with fairly lower friability values. Also, no significant changes in the disintegration time, hardness or friability were observed on storage at different conditions. Both sodium CMC formulations were found to be unsatisfactory since they exhibited capping. Moreover, tablets containing a higher moisture content were slightly discoloured after four weeks of storage at 45° and 55°C.

Moderately hard tablets with short disintegration times were obtained when using starch as binder, however, varying hardness and friability values were observed at different moisture levels. Formulations containing a lower moisture content gave harder tablets with correspondingly lower friability values. Moreover, a higher moisture level was associated with a greater tendency for capping. Storage of those tablets at a higher temperature and relative humidity was associated with a marginal increase in the hardness of both formulations, however, no apparent changes in friability

were observed. The disintegration time was also unaffected by storage at different conditions. This is in accordance with the results obtained by Alam and Parrott (25) where no variations in disintegration of starch tablets was observed.

Tablets compressed from ethocel granulations showed no moisture dependency. The disintegration time, hardness or friability were unaffected by the amount of moisture included. Also, the disintegration times of these tablets were fast and showed no apparent changes with time or storage conditions. The ethocel formulations gave moderately hard tablets. The hardness was unchanged at all storage conditions, however, the friability slightly increased on storage. Moreover, formulations containing lower moisture showed unacceptably high friability values when stored at higher temperatures. Yellow discolouration and spotting on tablet surfaces previously observed with other binders were not exhibited by both ethocel formulations even at higher storage temperatures, however, these tablets at both moisture levels showed fairly high degrees of capping and lamination when kept at all storage conditions.

The disintegration time of tablets obtained using methocel as binder was slightly higher than that using

ethocel. Also, the hardness was significantly higher with a correspondingly lower friability. Consequently, better tablet properties were obtained using methocel as binder. Furthermore, the methocel formulation containing a lower moisture content gave slightly harder tablets, however, the friability was apparently unaffected. Storage of these tablets at different conditions of temperature and humidity for periods upto sixteen weeks had no noticeable effect on disintegration, hardness or friability. Moreover, the two methocel formulations at both moisture levels exhibited no apparent capping or lamination. The yellowish discolouration and spotting were also not observed in either formulation.

On the basis of the above results several conclusions of some practical relevance could be arrived at. The use of starch, ethocel or sodium CMC in the formula adopted in this investigation gave unsatisfactory tablets because of their high friability levels and their ready tendency for capping. Furthermore, unacceptably high disintegration times were obtained, particularly at higher storage temperatures, when PVP was used as binder.

Although, satisfactory disintegration, hardness and friability values were obtained with gelatin for-

mulations, capping and lamination observed in tablets formulated with a lower moisture content, as well as, the yellow spotting and discolouration of the higher moisture formulation make gelatin unsuitable for use.

Finally, granulation with methocel yielded satisfactory tablets with acceptable disintegration time, hardness and friability and were unaffected by storage at different conditions of temperature and humidity. Moreover, they showed no capping or surface discolouration and spotting even at higher storage temperatures.

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