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EFFECT OF PARTICLE SIZE, CONTENT IN LUBRICANT, MIXING TIME AND STORAGE RELATIVE HUMIDITY ON DRUG RELEASE FROM HARD GELATIN AMPICILLIN CAPSULES.

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SUMMARY

The influence of several variables on the release of ampicillin from hard gelatin capsules is studied. 18 lots of ampicillin capsules were prepared, with the following affecting variables: a) time of mixing the materials before filling the capsules, b) ampicillin particle size, c) Content in lubricant (magnesium stearate), d) Storage under several humidity conditions. It was found that dissolution rate is significantly affected by the size of ampicillin particles. Similar effects by variation of the other parameters are observed.

INTRODUCTION

Drug release of several dosage forms has been the subject for study of many investigators. Several methods and apparatus have been presented for this purpose (1-4). Also, standards on drug release

controls, for several formulae are described in several Pharmacopoeias (5).

Drug release is a property of great importance for a dosage form, as it is related to its bioavailability.

Ampicillin is a substance that may present variations of its bioavailability and thus become less effective pharmaceutically (6). For hard gelatin capsule forms of ampicillin, USP XX requires a release of 75% of the total substance within 45 minutes of dissolution (5).

In the present work, several parameters affecting the release of ampicillin from hard gelatin capsules are investigated.

These parameters concern the **preparation** of the dosage form (particles size of the drug, percentage of lubricant, time of mixing materials before filling the capsules) and then **storage** under specific conditions of humidity.

MATERIALS AND METHODS

Ampicillin trihydrate compact* crystalline, hard gelatine capsules No 0, lactose 80 and 200 mesh (BDH, *grade pure*) as additional substance, and magnesium stearate (BDH, *grade pure*) as lubricant were used for the preparation of the capsules.

A complete serie of Endecotts Ltd, England, sieves were used for the sieve analysis of the pure ampicillin.

A Fritsch ball mill type 06 - 102 was used to obtain a fraction of ampicillin with particles under 100 μm.

Mixing of the materials was made with a Turbula mixer (Suiss) type 12C.

Capsules were filled through a Feton (Belgium) capsule filling manual apparatus.

A 6ply USP XX rotating basket apparatus, was used for the dissolution test of the capsules, type 6454 - 230 (Hanson Research

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* *Courtesy of Bristol Europe SpA, Sermonetta Italy, through Bristol Hellas, S.A.*

Corporation, U.S.A.), was used for the dissolution test of the prepared capsules.

A Perkin-Elmer Hitachi model 200 spectrophotometer was used for measuring the absorbance of the samples.

EXPERIMENTAL

A sieve analysis of pure ampicillin was carried out, to give several particle fractions. The results of this analysis are shown on table 1. It is noted that in order to obtain particles below 100 μm, a quantity of pure ampicillin was milled with a ball mill.

The formulas for the preparation of the capsules are shown on table 2. These formulas were prepared with ampicillin with particles of size a) under 100 μm, b) 300/600μm, and c) with pure ampicillin. All nine lots of table 2, were prepared twice, for mixing time 2 and 10 minutes (Lots "A" and "B" respectivelly), giving a total of 18 lots of capsules.

Weight variation

After the preparation of the capsules, a weight control was applied on 20 capsules of every lot. The results are shown on Table 3. It was concluded that the prepared capsules were according to the requires of USP XIX (7).

Storage

A number of capsules from every lot, was stored in sealed containers of relative humidity 50%, 75% and 90%, for study after 4 months. Standard relative humidity was obtained with glycerin-water solutions as follows: For relative humidity 50%, 3.900 gr of glycerin with 1.100 gr of water, for 75%, 2.900 gr glycerin and 2.100 gr water, for 90%, 1.750 gr glycerin and 3.250 gr water (1).

Reference curve

Six standard solutions of 20, 40, 50, 70, 80 and 100 mg ampicillin in 100 ml HCl 0,1N, precisely weighed and completely dissolved by magnetic stirring, were prerared for the layout of the reference curve. A linear regression analysis of the data has shown that the

Table 1. Granulometric analysis of pure ampicillin

granule size (μm)	%
>600	14.64
500-600	24.70
300-500	12.00
250-300	6.81
212-250	10.10
180-212	1.35
150-180	14.88
125-150	13.25
106-125	2.32

Table 2. Formulas and lots of capsules prepared

LOTS	1	2	3	4	5	6	7	8	9
Ampicillin <100μm	a	a	a						
Ampicillin 300-600μm				a	a	a			
Ampicillin pure							a	a	a
Lactose 80 mesh	0.1a	0.1a	0.1a						
Lactose 200 mesh				0.1a	0.1a	0.1a	0.1a	0.1a	0.1a
Mg Stearate	0.002a	0.006a	0.12a	0.002a	0.006a	0.12a	0.002a	0.006a	0.12a

method is linear: R=0,9999, SE 0,016, slope 6,95, intercept -0,25. Standard solutions for the reference curve as all the other samples were measured at the spectrophotometer at 261 nm.

Content Uniformity

To determine the exact content of every lot in ampicillin, a content uniformity test was applied in all lots of capsules (6, 8). The test consisted of a complete dissolution, by magnetic stirring, of five capsules, each in 500 ml of HCl 0,1N, and then measuring

Table 3. Weight control of the prepared capsules

LOT	Weight of 20 capsules (gr)	Mean weight (gr)	S.D.	S_{rel}
1A	7.17	0.3585	0.01348	3.7614
1B	6.77	0.3385	0.00875	2.5852
2A	6.44	0.3220	0.00895	2.7770
2B	6.86	0.3430	0.01260	3.6756
3A	6,75	0.3375	0.01251	3.7070
3B	6.74	0.3370	0.01559	4.6270
4A	12.52	0.6260	0.01231	1.9667
4B	12.31	0,6155	0.01050	1.7060
5A	12.11	0.6055	0.01099	1.8150
5B	12.02	0.6010	0.07788	1.3112
6A	11.97	0.5985	0.00670	1.1208
6B	11.94	0.5970	0.00813	1.3422
7A	10.41	0,5205	0.01637	3.1461
7B	10.31	0.5155	0.00944	1.8322
8A	10.12	0.5060	0.00995	1.9658
8B	10.54	0.5270	0.01311	1.9565
9A	10.16	0.5080	0.01281	2.5255
9B	10.02	0.5010	0.01334	2.6622

the absorbance at 261 nm. The mean value was considered to be the content in ampicilin of the lot. Results are shown on table 4.

Dissolution test.

It was applied on a 6ply USP XX rotating basket apparatus (6). The study was carried out at 37°C 0.1, in 900 ml of HCl 0,1N. Four capsules from every lot were measured. Samples were taken at 5, 10, 15, 30 and 60 minutes. The results are shown on Table 5.

Table 4. Content uniformity test on the 18 lots of capsules

Lot	Weight* (mg)	True value** (mg)	Declared value(mg)
1A	238	256	250
1B	238	252	250
2A	222	227	250
2B	243	242	250
3A	237	246	250
3B	237	233	250
4A	526	470	500
4B	515	470	500
5A	505	526	500
5B	501	588	500
6A	498	587	500
6B	597	517	500
7A	420	420	400
7B	415	386	400
8A	406	402	400
8B	427	418	400
9A	408	429	400
9B	401	415	400

* Mean value of 20 capsules; from the weight of every capsule 100mg were substracted, being the standard weight of empty capsules. So numbers of the table concern net content weight.

** Values found spectrophotometrically. The test was applied on 5 capsules of every lot.

RESULTS AND DISCUSSION

Table 6 presents a series of dissolution tests applied on all lots of capsules, including those stored under several relative humidity conditions.

From the results of this table, it is concluded that the granule size of ampicillin is mainly related to the dissolution rate (lots 1-6). Lubricant influence appears in "0.006a" lots, while further increase of the content of the lubricant (to 0.12a), yields no further increase of the dissolution rate. See lots 1A-2A, 1B-2B, 4A-5A.

Table 5. Results of dissolution test on the capsules prepared.

Lot	Drug release (in mg)				
	5′	10′	15′	30′	60′
1A	37	107	170	249	277
1B	25	79	137	217	259
2A	115	207	209	230	259
2B	145	210	224	243	247
3A	82	200	225	238	262
3B	124	230	232	248	272
4A	282	323	390	433	475
4B	264	363	406	414	463
5A	307	408	423	545	494
5B	185	357	423	462	501
6A	339	396	462	490	526
6B	17	165	342	396	472
7A	202	318	345	351	441
7B	231	317	346	331	375
8A	211	361	366	396	418
8B	376	368	372	386	414
9A	283	392	400	417	440
9B	313	371	367	376	416

Table 6. T75% for the lots of the capsules prepared and those stored for 4 months in several relative humidity conditions.

LOT	Ampicillin granules (μm)	Lactose granules (mesh)	Mg Stearate (xAmpicillin)	Mixing time (min)	T75% (min)	T75% of caps. stored for 4 months (min) Storage relative humidity 50%	75%	90%
1A	<100	80	0.002	2	18	36	29	NR*
1B	<100	80	0.002	10	25	14	24	NR
2A	<100	80	0.006	2	9	39	44	NR
2B	<100	80	0.006	10	8	11	23	NR
3A	<100	80	0.12	2	9	14	45	NR
3B	<100	80	0.12	10	8	13	33	NR
4A	300-600	200	0.002	2	14	25	45	36
4B	300-600	200	0.002	10	12	13	40	16
5A	300-600	200	0.006	2	8	28	28	22
5B	300-600	200	0.006	10	12	5	40	26
6A	300-600	200	0.12	2	9	15	23	25
6B	300-600	200	0,12	10	25	4	24	20
7A	pure Amp.	200	0.002	2	8	10	10	12
7B	pure Amp.	200	0.002	10	8	12	15	10
8A	pure Amp.	200	0.006	2	8	10	13	12
8B	pure Amp.	200	0.006	10	3	18	13	13
9A	pure Amp.	200	0.12	2	6	30	14	13
9B	pure Amp.	200	0.12	10	4	30	14	15

* NR = The release of ampicillin was much lower than 75%.

In lots with small particle (granule) size (<100 μm) and a small lunricant quantity (0.002a) a negative effect of the mixing time on the dissolution rate is observed. An analogous influence is observed in lots with granule size 300-600 μm. However this factor is not affected by the lubricant.

In pure ampicillin lots, no significant effects of either mixing time or lubricant are observed.

Humidity influence on dissolution rate is higher at small particles (<100 μm). This can be clearly seen in lots stored at 90% relative humidity. Much less than 75% of the drug contained is released after 45 minutes of dissolution. (lots characterised by NR=no release). This behaviour of lots 1,2,3, can be explained by the suggestion that small particles of the drug (being the 90% of the mixture), are strongly agglomerated, resulting a significant reduce of the dissolution rate.

It is clear, that pure ampicillin, containing all particle sizes, presents a more stable dissolution rate and, resistance to the variables applied in this experiment.

CONCLUSIONS

It is concluded that the main factor affecting the liberation of ampicillin is the particle size, as all lots of large particles had a better T75%. Lubricant appears to be a less affecting agent. The above conclusion explain proper T75% of pure ampicillin, as its content in large particles is high. This is confirmed from the granulometric analysis.

Mixing time does not affect T75% of pure ampicillin brands, while it partially affects the rest of the lots.

Humidity causes a distinct increase of T75% on lots of small particles, while no significant increase of the same is observed in pure ampicillin brands.

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