Bull. Pharm. Sci., Assiut University
Vol. 6, Part 2, PP. 387-398

FORMULATION AND IN-VITRO EVALUATION OF RIBOFLAVIN TABLETS PREPARED BY FLUIDIZED BED GRANULATION TECHNIQUE

M.A.A. Kassem[*], A.T. Nouh[**], T.El-Bayomy[***] & Alaa.A.A. Kassem[****]

Department of Pharmaceutics, Faculty of Pharmacy, Cairo University[*], Faculty of Pharmacy, Mansoura University, Mansoura[**], National Organization for Drug and Research, Giza, Egypt[***] and Faculty of Pharmacy, El-Azhr University Nasr City, Egypt[****]

Spray granulation technique using fluidized bed was used for preparing riboflavin granules. Five binders were used for granulation as spray liquids, Polyvinylpyrrolidone proved to be the most suitable binder followed by sodium alginate and sodium carboxy methyl cellulose. Methyl cellulose produced tablets which disintegrated within the U.S.P.XX. limit, but of low dissolution rate; while ethyl cellulose gave tablets which did not conform to the official limit, but the drug was released from the tablet matrix faster than from tablets prepared by methyl cellulose.

Moist Granulation technique is widely employed for tablet preparation, but it has many drawbacks[1-3]. Granulation by fluidized bed technique proved to be more convenient method especially in case of thermolabile material, since the granulation procedure can be carried

out at a temperatures only slightly above ambient (about 40°).

Many authors found that granulation by fluidized bed technique reduced processing time, improved granules and tablet properties, and gave better drug release and higher bioavailability[4-7].

The object of this study was a trial to make use of the fluidized bed granulation technique for the preparation of riboflavin tablets. Several binders were employed to find out the most convenient binder for preparing a suitable tablet with acceptable physical properties . The relation between the type of binder and the dissolution behaviour of riboflavin tablets was also investigated.

EXPERIMENTAL

Materials:

Riboflavin; U.S.P.XIV, Tareda Chemical Ind. L.T.D. Osaka, Japan, Sodium alginate, the General Chemical & Pharmaceutical Co. Ltd., Sudbury., Polyvinylpyrrolidone, Plasdone, General Aniline & Film Corp., N.Y.-Potato starch, Magnesium stearate, Methyl cellulose M320, Sodium carboxy methyl cellulose and ethyl cellulose were kindly supplied by CID Pharmaceutical Co. Cairo

Apparatus:

Uniglatt " Wurster" System, CH-4133, Bunzen-Haltingen, West-Germany, Erweka Tablet Compression Machine, Erweka Tablet Hardness Tester, Erweka Friabilator, Erweka Tablet Disintegration Apparatus and Erweka dissolution tester, Erweka-Apparatebeau, Frankfurt, Germany, Baty Dial Micrometer Model 120-1206 (Baty & Co. Ltd., Sussex, England.)

Procedures:

A- Preparation of Tablets:

1- Formulation: Tablets were prepared containing in each 5 mg of riboflavin made up to total weight of 150 mg with binder, lubricant, disintegrating agent, and filler. The filler used was potato starch. 2% sodium alginate in water, 2% methyl cellulose in water, 3% sodium carboxy methyl cellulose in water, 5% ethyl cellulose in alcohol and 3% polyvinylpyrrolidone in alcohol were used separately as binders. 5% starch was used as disintegrant and 3% stearic acid as lubricant.

2- Preparation of the granules: Riboflavin was mixed with the calculated amount of starch as diluent according to the geometric dilution method. The whole powder was introduced into the conical container of the glatt apparatus. The mixing process was continued for about 5 minutes with the aid of air stream fluidized from below. The exhaust filter was shaken from time to time to keep all the powder inside the container and to ensure the proper ,mixing. After adjusting the atomized compressed air at 29 psi, the binder solution was sprayed over the bed. The spray

liquid pump was adjusted to give a suitable droplet size from the binder solution. The temperature was maintained at 60° during the granulation process. 200 ml of binder solution was found to be sufficient to produce well developed granules. After consuming the granulating liquid, the product was left to fluidize inside the apparatus for about 15 minutes for complete drying at the same temperature.

3- Compression: The mixed granules, potato starch and stearic acid were well mixed and compressed into flat tablets, each weighing about 150 mg.

B- Evaluation of Tablets:

Tablets were evaluated for uniformity of weight (B.P. 1980), uniformity of thickness, hardness(Erweka), friability (Erweka), disintegration time(B.P.)according to the previously published procedures by Sakr et al[8] and disolution rate using 500 ml distilled water. One tablet was placed in the basket which was allowed to rotate at a rate of 100 r.p.m. Samples of solution were withdrawn, meanwhile, an equivalent volume of distilled water was added. Samples were analyzed by measuring the absorbance spectrophotometrically at 445 nm[9].
Data acquired were treated Kinetically as shown in Table 2 and Fig. 1 (A & B).

RESULTS AND DISCUSSION

Uniformity of Weight and Thickness: Spray granulation produced spherical, free flowing granules, thus all themanufactured tablets using different binders fulfilled the

requirement of the B.P. 1980 for weight uniformity. Measurement of the thickness was an additional control to the tablets dimensions and ensures reproducibility. The coefficient of variation of thickness never exceeded 2.33% which means excellent uniformity. The mean weight and thickness results are shown in Table 1.

Mechanical Strength:

The effect of different binders on the mechanical strength of the produced tablets as tested by hardness test and friability test, was studied. Polyvinylpyrrolidone and sodium carboxy methyl cellulose were better than sodium alginate and ethyl cellulose in producing more hard tablets, while methyl cellulose occupied intermediate position .

The friability results of all the manufactured tablets were similar and did not exceed 0.6% (Table 1).

Disintegration Time:

Tablets were tested for disintegration by the modified B.P. 1968 method suggested by Sakr *et al* [8]. It was found that all the manufactured tablets disintegrated within the U.S.P. XX. limit except those tablets prepared by ethyl cellulose which did not show any sign of disintegration for more than three hours. According to the disintegration time, the different binders can be arranged in the following ascending order: Polyvinylpyrrolidone < methyl cellulose < sodium alginate < sodium carboxy methyl cellulose.

Dissolution Rate: Data acquired were treated kinetically and was found to follow the first order equation (Table 2 and Fig. 1). Dissolution results revealed that the dissolution rate of the tested tablets depends on the type of

binder used. According to dissolution data, the tested binders can be arranged with respect to their effect on the dissolution rate after 15 minutes in the following sequence as shown in Table 1: Polyvinylpyrrolidone > sodium carboxy methyl cellulose > sodium aglinate > ethyl cellulose > methyl cellulose.

An identical result was obtained if we compare the T_{50} of the various tablets prepared by different binders as shown in Table 2.

On the other hand, a different pattern was obtained if we compare the disintegration time as shown in Table 1. Tablets prepared by ethyl cellulose did not disintegrate up to 180 minutes, yet 50% of the drug was leached out from the tablet matrix after 39 min. In contrast, tablets prepared by methyl cellulose disintegrated after 10 minutes, while 50% of the drug was released after 81 min. This can be explained by the observation of these tablets. Disintegration into large fragments occurred, but drug was kept embedded in the fragments. Polyvinylpyrrolidone can be considered the best binder for riboflavin tablet as regards its influence on dissolution, since it was the most effective binder in producing complete release of the drug in a short time. No reliable correlation can be established between disintegration and dissolution rate.

CONCLUSION

Spray granulation technique proved to be a suitable method for preparing tablet granules. The produced granules was highly flowable and had suitable cohesiveness, thus produced

tablets of proper uniformity of weight and thickness and good mechanical properties. All the produced tablets disintegrated within the U.S.P. XX. limit, except those tablets prepared by ethyl cellulose as binder. Tablets prepared by methyl cellulose showed low dissolution rate. Polyvinylpyrrolidone proved to be the most effective binder in producing tablets of suitable uniformity of weight and thickness, good mechanical properties and high dissolution rate followed by sodium carboxy methyl cellulose and then sodium alginate.

Table 1: Effect of various binders on the characteristics of riboflavin tablets prepared by spray granulation technique.

Binder	Weight[a] (g)		Thickness[a] (mm)		Hardness[b] (Kg)		Friability[c] (%)		Disintegration[b] Time (min.)	
	Mean	C.V.%	Mean	C.V.%	Mean	C.V.%	Mean	C.V.%	Mean	C.V.%
Poyvinylpyrrolidone	0.1182	1.5183	3.70	1.4978	5.43	9.48	0.57	28.97	9.08	11.62
Sod. Carboxy Methyl cellulose	0.1303	1.5570	3.63	1.9327	4.23	15.14	0.38	6.75	13.45	10.47
Sodium Alginate	0.1180	1.6032	3.25	1.5797	2.65	14.20	0.32	12.36	11.03	7.19
Ethyl Cellulose	0.1189	1.5412	3.05	2.3295	2.68	9.90	0.61	11.03	> 180	-----
Methyl Cellulose	0.1333	1.9788	4.63	0.8452	3.13	19.32	0.49	26.39	9.95	9.82

a = mean of 20 tablets; b = mean of 10 tablets; c = mean of 5 determinations, 20 tablets each.

Table 2: Effect of binder on the dissolution % of riboflavin from tablet matrix prepared by spray granulation technique.

Binder	Drug dissolution % after minutes										K min.$^{-1}$	T_{50}(min.
Polyvinylpyrrolidone	36.96	46.30	53.29	69.57	82.61.	88.52	93.57	95.65	96.84	98.00	0.04496	15.41
Sod. Carboxy Methyl Cellulose	31.51	39.74	49.88	66.12	75.46	83.70	89.28	93.45	95.83	97.11	0.03899	17.78
Sodium Alginate	28.95	36.84	44.74	66.12	78.95	85.55	91.68	94.73	96.84	97.76	0.03873	17.89
Ethyl Cellulose	11.14	14.85	27.55	38.34	55.33	63.29	72.46	77.61	81.34	84.15	0.01771	39.13
Methyl Cellulose	2.49	8.79	11.00	27.55	30.85	42.46	49.88	55.33	60.18	64.50	0.00857	80.82

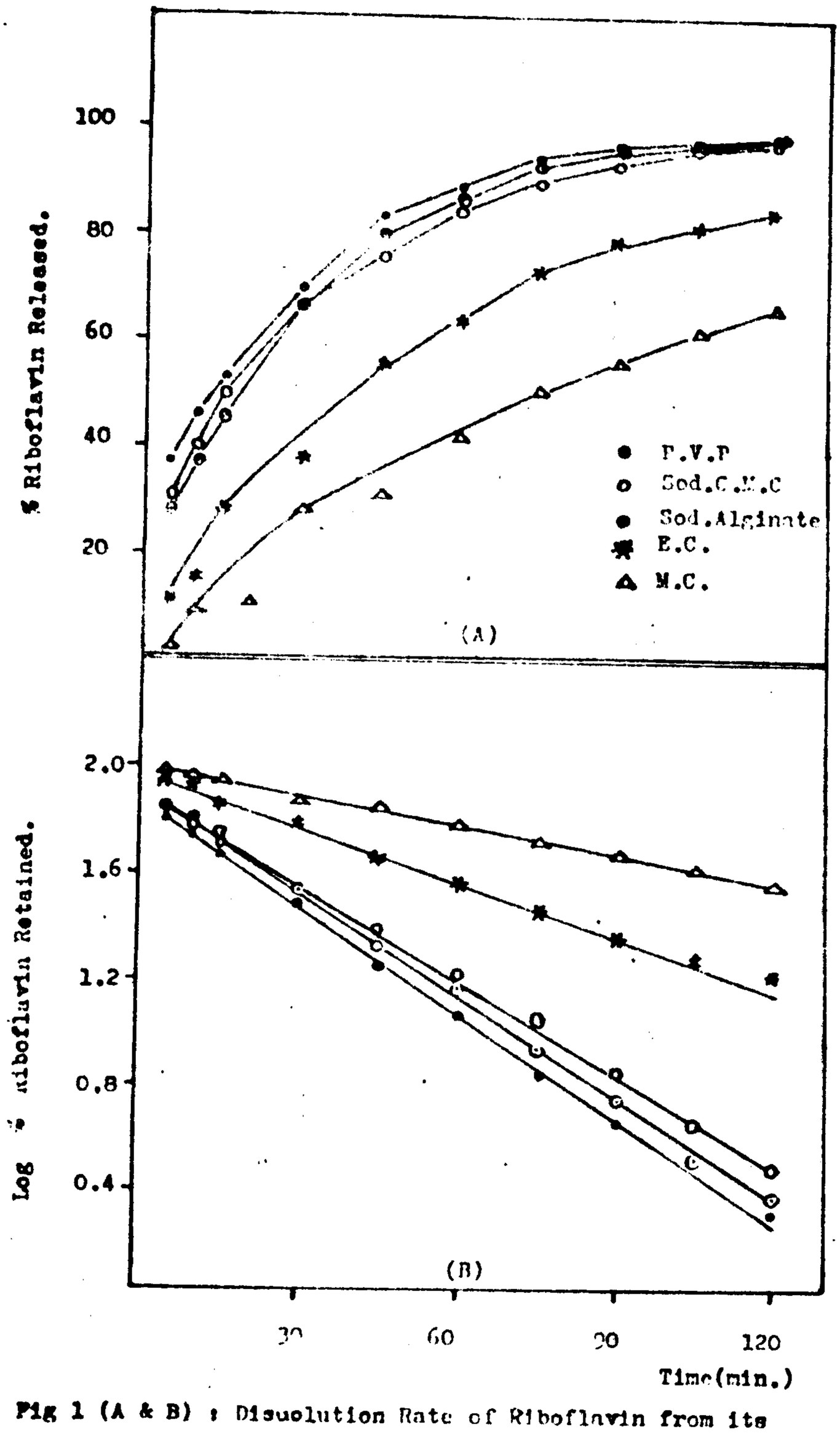

Fig 1 (A & B) : Dissolution Rate of Riboflavin from its Tablets Prepared by Different Binders.

REFERENCES

1) H. Seager; Manuf. Chem. Aerosol News, 48, 25 (1977).

2) W. Pietsch; Drugs made in Germany, 13 , 58 (1970)

3) D.N. Travers; J. Pharm. Pharmacol. 27, 516 (1975)

4) D.E. Wurster; J. Pharm. Sci., 49, 82 (1960)

5) M.W. Scott, M.A. Lieberman, A.S. Rankell and J.V. Batilsta; ibid, 53, 314 (1964).

6) A.S. Renkell, M.W. Scott, H.A. Lieberman, F.S. Chow and J.V. Batlista; ibid, 53, 320 (1964).

7) W. Erni, and F. Ritschel; J. Pharm. Ind., 39, 284 (1977).

8) A.M. Sakr, A.A. Kassem, S.A.A. Aziz and A.H. Shalaby; Canad. J. Pharm. Sci., 8, 6 (1978).

9) N. Wahba, and E. Fahmy; J. Pharm. Pharmcol., 17, 489 (1965).

صياغة واتاحة الريبوفلافين
من الاقراص المحضرة بطريقة التحبيب بالبرش

محمدعلىعلى قاسم-أحمدطلعت نوح - تهانى البيومى-علاء الدين على قاسم

تم فى هذا البحث تحضير اقراص الريبوفلافين من حبيبات محضرة بطريقة الرش باستخدام مواد رابطة مختلفة وقد وجد ان عديد فنيل البيروليدون هو المادة الرابطة المثالية يليه ألجينات الصوديوم كربوكسى ميثيل السليلوز فى حين اعطى ميثيل السليلوز اقراصا تتفتت فى زمن يطابق متطلبات دستور الادوية الامريكى ولكن معدل الاتاحة المعملية للمادة الدوائية كان بطيئا وعلى العكس من ذلك فان ايثيل السليلوز قد اعطى اقراصا لاتتطابق مع دستور الادوية الامريكى من حيث زمن التفتت ، بينما معدل اتاحة المادة الدوائية كان اسرع من الاقراص المحضرة بميثيل السليلوز كمادة رابطة .

received in 25/11/1982 & accepted in 16/12/1982