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A STUDY ON THE POWDER, TABLETING AND STABILITY CHARACTERISTICS OF CELLACTOSE AND OTHER SELECTED DIRECT COMPRESSION EXCIPIENTS

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تم فى هذا البحث دراسة ومقارنة خواص كل من السلاكتوز ، التابلتوز ، لاكتوز ، آفسيل ١٠١ وقد أستخدمت هذه الصواغات بالإضافة إلى خليط من الآفسيل واللاكتوز بنسبة ٣:١ فى تحضير أقراص الجليبنكلاميد بطريقة الكبس المباشر. ثم تلى ذلك دراسة الخواص الطبيعية للأقراص والمحتوى الدوائى ومعدل الإتاحة قبل وبعد تخزين هذه الأقراص عند درجة حرارة ٤٠° ودرجتى رطوبة نسبية ٣٠ ٪ ، ٨٠ ٪ لمدة ١٦ ، ١٢ أسبوعا على التوالى.

وقد أظهرت النتائج أن أنسيابية اللاكتوز هى الأفضل يتبعها التابلتوز والسلاكتوز ثم الآفسيل. كما أنتج التابلتوز أقراص هى الأفضل من ناحية تجانس الوزن قبل وبعد التخزين.

وأثبت السلاكتوز أنه الأفضل فى الحفاظ على حجم ومحتوى الدواء للأقراص بعد التخزين. أما الآفسيل فكان هو الأفضل فى الحفاظ على معدل إتاحة الأقراص أثناء مدة التخزين يتبعه السلاكتوز ثم خليط الآفسيل : اللاكتوز (٣:١).

The powder characteristics of the direct compression excipients Cellactose, Tablettose, spray dried lactose (SDL) and Avicel PH101 were compared. These excipients and a mixture of Avicel:SDL (1:3) were used for the preparation of glibenclamide tablets. The tablet characteristics, including the physical properties, average drug content, as well as the dissolution rate were evaluated before and after the tablets were subjected to storage under two accelerated conditions: 40°C/30% relative humidity (RH) for 16 weeks and 40°C/80% RH for 12 weeks.

The results showed that SDL has the best flow properties followed by Tablettose, Cellactose and Avicel. With regard to tablet characteristics, Tablettose produced tablets with the least weight variations before and after storage at both low and high relative humidity, while a mixture of Avicel:SDL (1:3) produced tablets that gave the highest values. Cellactose was the best vehicle in preserving the tablet size and glibenclamide content during storage. On the other hand, the least changes observed in the dissolution profiles of glibenclamide tablets due to storage was found for tablets made of Avicel followed by these of Cellactose and a mixture of Avicel:SDL (1:3).

INTRODUCTION

The direct compression tableting process was made possible by the commercial availability of directly compressible excipients.[1] Many direct compression excipients are now prepared by a co-processing procedures from two or more components. Such mixture can combine the good characteristics in each component for the advantage of direct tableting. Cellactose is one of these excipients, which composed of 25% powdered cellulose and 75% α-lactose monohydrate in a one body compound with a granular shape.[2]

The aim of this study was to investigate the flow and packing characteristics as well as the tablet properties produced using Cellactose as a direct compression excipient and glibenclamide as a model drug. These characteristics were compared with those produced using Avicel, spray dried lactose (SDL), Tablettose and a mixture of Avicel : SDL (1:3). The effect of

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these excipients on the tablet properties was also studied when the tablets were stored under different stress conditions.

MATERIALS AND METHODS

Cellactose and Tablettose are gifts from Meggle, Wasserburg, Germany, Avicel PH101 and Spray dried lactose (SDL) are from Winlab ltd., Maidenhood, Berkshire, UK. Micronized Glibenclamide was supplied by the Saudi Pharmaceutical Industries and Medical Appliances Corp. (SPIMACO), Saudi Arabia. All materials were used as received.

Powder characteristics

The average particle size was determined using a standard set of sieves and a shaker. The bulk density (g/ml) was determined using a 250 ml graduate cylinder and a suitable weight of the given powder, while the tap density (g/ml) was determined after tamping the cylinder on a wooden surface until a constant volume was obtained. The values measured were the average of five determinations. Derived parameters, such as the Hausner factor and percent compressibility were calculated. The angle of repose "θ" and the flow rate (g/sec) for each powder were determined according to Wells.[3]

Preparation of tablets

four single direct compression excipients and the physical mixture of Avicel with SDL at the ratio of 1:3 were used to produce tablets according to the following general formula:

Glibenclamide	4.17%
Excipient	94.83%
Magnesium stearate	1.00%

Mixing of the drug and the excipient was carried out by a serial mixing procedures on a glass tile for at least 5 minutes in each step. This was followed by a tumble mixing for 15 minutes. Magnesium stearate was then added to the blend and mixed for another 5 minutes. A single punch tablet machine (Erweka G.m.b.H., Type EKD, Germany) was used to produce 6.4±0.01mm tablets having an average weight of 0.12 g and hardness from 3 to 8 kg on Erweka Hardness Tester.

Evaluation of tablets

1- Physical properties: The manufactured tablets were evaluated with regard to their uniformity of weight (20 tablets), uniformity of thickness (20 tablets) using micrometer (Model Mitutoyo, Japn), hardness (6 tablets) using Erweka hardness tester (type TBH 28, Germany), disintegration time (6 tablets) using Erweka disintegration apparatus (type ZT4, Germany) in distilled water at 37°C with discs.

2- Determination of average drug content: The average glibenclamide content was determined by powdering five tablets in a mortar. An amount equivalent to 5.0 mg glibenclamide was extracted using ethanol. After centrifugation at 3000 rpm for 10 minutes, the supernatant was separated and the drug was determined spectrophtometrically at 300 nm (Perkin Elmer 555, USA).

3- Dissolution rate: The dissolution rate studies were performed in a 6 units, tablet dissolution testing system (Caliva, England). The test was conducted at 37°C±0.5 following the USP XXIII method 2 (paddle) at 100 rpm using 900 ml distilled water as the dissolution medium. Glibenclamide concentrations were monitored spectrophotometrically at 300 nm and the average readings of six samples was recorded for each formula at different time intervals.

Storage of tablets

Tablets from different batches were packed in amber coloured glass containers with plastic caps on and placed in closed desiccators containing saturated salt solutions giving rise to 30% (low) and 80% (high) relative humidity (RH) when kept in incubators (Heraus 6060, Germany), maintained at 40°C for different time periods. Re-evaluation of the tablet properties

was performed after 1, 6 and 12 weeks for those stored at 80% RH and at 4, 7 and 16 weeks for tablets stored at 30% RH.

RESULTS AND DISCUSSION

Powder characteristics

The average particle size for the single excipients used in this study are shown in Table 1. It was found that Tablettose and Cellactose have the same average particle size, twice as much as those of Avicel and SDL. Table 1 also shows the flow and the density characteristics of the powders along with the derived parameters. It was found that the angle of repose of SDL, Cellactose and Tablettose has an equal value (~30), which indicate a good to passable flow properties to those powders.[3] In spite of the similar values of the angle of repose for the three excipients, the flow rate was found to vary among them. The flow rate of Tablettose was close to that found earlier by Mitrevej *et al.*[4] The flow rate is considered as a direct measure for the powder flow characteristics. Therefore, SDL with the highest flow rate value was considered to be the best direct compression excipient among the studied powders in this respect. The angle of repose and the flow rate of Avicel could not be determined because the powder did not flow through the funnel orifice in this experimental set up. This poor flow characteristics of Avicel PH101 was further confirmed from the Hausner index value calculated from the bulk and tapped densities (Table 1). This is in agreement with the conclusion of Doelker.[5] The Hausner index values for the other excipients studied, however, were less than 1.25, indicating minimum inter particulate friction and good flow. The percent compressibility (Carr' index) for the studied excipients exhibited the same trend in magnitude as the Hausner index and the angle of repose.

Table 1: Measured and derived parameters for the studied direct compression powdered excipients.

Property	Avicel	Spray dried lactose	Tablettose	Cellactose
Average particle size (um)	96.68	87.76	189.24	192.52
Angle of repose ±SD	-	30.00± 0.45	31.95± 0.73	31.94± 0.25
Flow rate (g/s) ±SD	-	19.55± 0.75	16.46± 1.96	9.84± 0.86
Bulk density (g/ml) ±SD	0.332± 0.002	0.676± 0.006	0.567± 0.01	0.379± 0.012
Tap density (g/ml) ±SD	0.503± 0.005	0.825± 0.012	0.690± 0.02	0.470± 0.013
Hausner factor	1.520	1.220	1.217	1.24
% Compressibility	34.04	18.10	17.83	19.40

Tablet characteristics

Tablets produced using different excipients at constant machine settings were evaluated for weight and thickness variations as well as for hardness, disintegration time, average drug content and dissolution rate. The results showed that the highest variations in weight was found in case of the mixed vehicle Avicel : SDL, (SD= ±5.1), which may be attributed to the difference in the density and the rate of flow between the two excipients. On the other hand, the smallest weight variation was found in case of Tablettose. There was no relationship between the weight variation and the flow properties of the studied vehicles. This agrees with the results of Pearls *et al.*[6]

Thickness of tablets is usually measured to control tablets dimensions and to ensure reproducibility. It was found that Avicel tablets have the highest inter-tablet thickness variations (SD= ±0.11). This is may be due to its poor flowability properties.

The hardness of the tablets were found to decrease in the following order: Avicel > Cellactose > SDL > Tablettose > Avicel : SDL (1:3). The results indicated that the hardness of tablets made from Cellactose is much higher than that made of a physical mixture of Avicel and SDL of the same composition, i.e. 1:3. Thus, it seems that the special treatment made in preparing Cellactose has improved some of its characteristics.

The disintegration time of glibenclamide tablets was within one minute, with large variations among different types of excipients. Avicel tablets exhibited the fastest disintegration and Tablettose tablets the slowest. This small disintegration time in case of Avicel was attributed to the fast aqueous penetration into compacts caused by breaking of H-bonds and subsequent widening of the pores, Lerk *et al.*[7] The results also showed that the disintegration times are independent of the hardness of the tablets.

The dissolution data of glibenclamide tablets formulations measured before storage are presented in Figure 1. An average of about 80% of the drug was released in one hour in all excipients. This is may be due to the water insolubility of glibenclamide. This phenomena was also observed by Schmidt and Rubensdofer.[8] The slow rate of dissolution found in case of Tablettose was explained by Mitrevej *et al.*[4] who found that the dissolution of Tablettose based tablets is by erosion rather than by disintegration of the base. The t_{50}% values (times for 50% of the drug to dissolve) were found to range from 10 minutes for SDL to 24 minutes for Tablettose, with the other excipients lying in between.

Stability studies

The effect of different excipients on the physico-chemical properties of glibenclamide tablets upon storage at 40°C/30% RH (low) and 40°C/80% RH (high) was studied. A change within ±5% in tablet weight was found with all the studied excipients. However, an increase in the thickness of tablets was observed, especially under high % RH conditions. The percentage increase was calculated and a mixture of Avicel : SDL (1:3) was found to have the highest percentage increase (24.14) followed by Tablettose (21.2), SDL (19.9), Avicel (6.13) and then Cellactose containing tablets (1.53) after storage at high % relative humidity conditions for 12 weeks. This increase in tablet thinkness is due to moisture pickup by the excipients. Both Avicel and SDL were found to absorb water when stored under high % RH conditions. The total amount of sorbed water is proportional to the fraction of amorphous material present in the solid.[9,10] However, the co-processed Cellactose has a lower ability to absorb moisture relative to a powder mixture of Avicel and SDL at the same composition. This can be due to the interaction and the possible alteration of the components of Cellactose during its preparation.[2]

The type of excipient had an effect on the hardness of the tablets upon storage at both low and high % relative humidity (Table 2). A decrease in hardness in tablets made with Avicel with time was observed and was more significant at high % RH.

Table 2: Effect of storage conditons on the hardness (H) and disintegration time (D.T.) of glibenclamide tablets made of various excipients.

Excipient Type	Storage Conditions													
	Initial		40°C/30% RH						40°C/80% RH					
			4 wks		7 wks		16 wks		1 wks		6wks		12 wks	
	H (kg)	D.T (sec)	H (kg)	D.T (sec)	H (kg)	D.T (sec)	H (kg)	D.T (sec)	H (kg)	D.T (sec)	H (kg)	D.T (sec)	H (kg)	D.T (sec)
Avicel	5.2	1.7	4.4	4.8	4.5	4.7	4.6	12.5	4.0	1.8	3.7	2.0	4.0	6.7
SDL	4.3	40.3	4.8	125.3	4.6	101.7	4.7	111.0	6.5	360.0	5.4	556.7	5.9	835.0
Tablettose	3.5	56.7	5.2	118.3	4.2	45.0	4.5	28.1	8.5	420.0	6.4	775.0	9.9	922.3
Cellactose	4.9	31.2	5.9	45.3	6.7	64.0	5.2	14.5	5.03	19.5	7.8	20.2	8.6	46.7
Avicel:SDL (1:3)	2.8	10.0	3.2	5.5	3.5	4.3	2.3	9.8	2.6	7.3	2.5	6.3	1.8	14.5

This was attributed to moisture absorption and loosening of inter particulate H-bonds.[11] This is in agreement with the results of Nikolic *et al.*[12] An increase in hardness was found in case SDL under high % RH conditions. Gordon *et al.*[13] found that lactose containing tablets showed a continuous increase in hardness after storage for 8 weeks at 37°C/80% RH. An increase in tablet crushing strength of tablets made of SDL after storage at 57% RH was also noticed.[10] This increase was attributed to crystallization of the amorphous part of lactose powder. A significant increase in hardness of tablets made from Tablettose and Cellactose was found, specially after storage at high relative humidity (Table 2). A physical mixture of Avicel : SDL (1:3) exerted a different pattern on the tablet hardness, where a slight decrease was observed upon storage under high relative humidity, while under low RH a small increase was observed after 7 weeks, followed by a decrease at the 16 week point.

A non-significant change in the disintegration time was seen in general due to storage except in case of SDL and Tablettose, where a marked increase was found, particularly on storage under higher RH. This increase correlates, at least in part with tablet hardness.

The average glibenclamide content before and after storage was determined. The pre-storage drug content was within 5% of the theoretical load in all cases. After storage for twelve weeks under high RH, Cellactose proved to be the best vehicle in stabilizing glibenclamide, while Avicel was the worst. Nikolic *et al.*[12] found that the greatest instability for acetyl salicylic acid formulation was that containing Avicel as an excipient when stored at 76% RH. This may be due to the high water content of Avicel. On the other hand, at low RH, a mixture of Avicel : SDL (1:3) was the only excipient that kept the average drug content within the 5% limit.

The dissolution profiles of glibenclamide tablets after storage are shown in Figures 2 to 6. The general pattern showed that tablets made of Avicel are least affected by storage both at low and high RH. This was followed by a mixture of Avicel : SDL (1:3), Cellactose, SDL, and the greatest change was for tablets made of Tablettose excipients.

A small decrease in dissolution rate from that of time zero was found in case of Avicel tablets at low and high RH. On the other hand, the dissolution profiles for other excipients showed a slight initial increase in dissolution after one week followed by a decrease with an extent depends on the type of vehicle used in

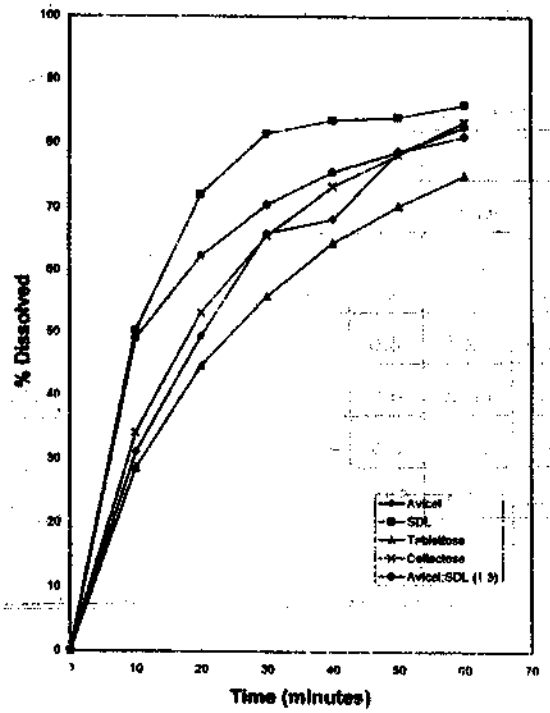

Fig. 1: Dissolution rate profiles of glibenclamide tablets made of different excipients (before storage).

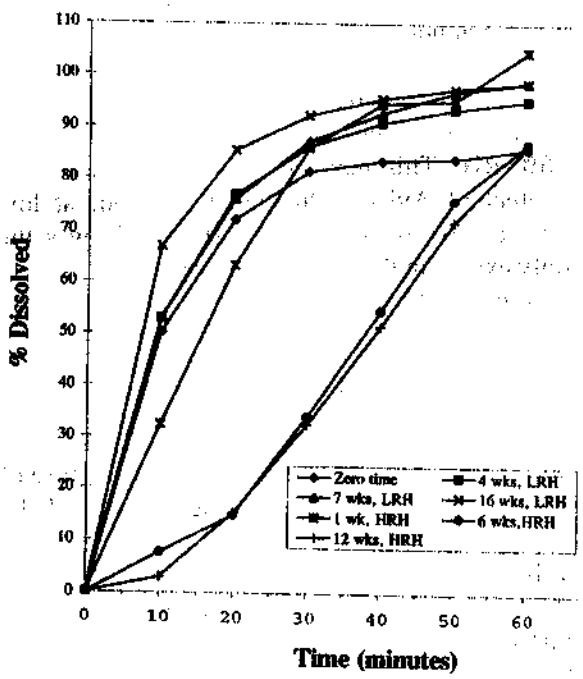

Fig. 2: Dissolution rate profiles of glibenclamide tablets using Spray dried lactose before and after storage under accelerated conditions.

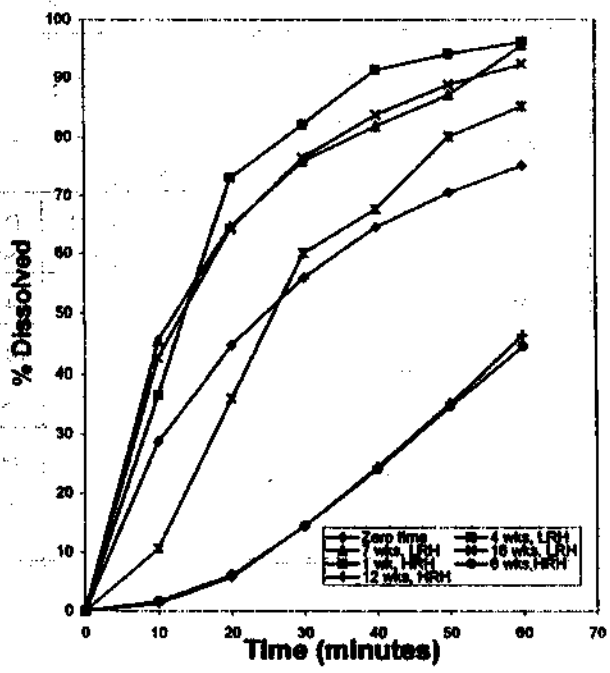

Fig. 3: Dissolution rate profiles of glibenclamide tablets using Tablettose before and after storage under accelerated conditions.

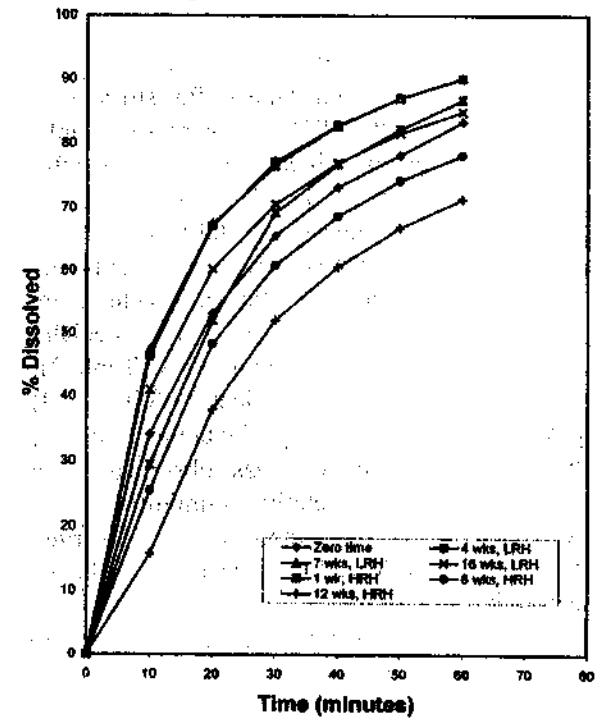

Fig. 4: Dissolution rate profiles of glibenclamide tablets using Cellactose before and after storage under accelerated conditions.

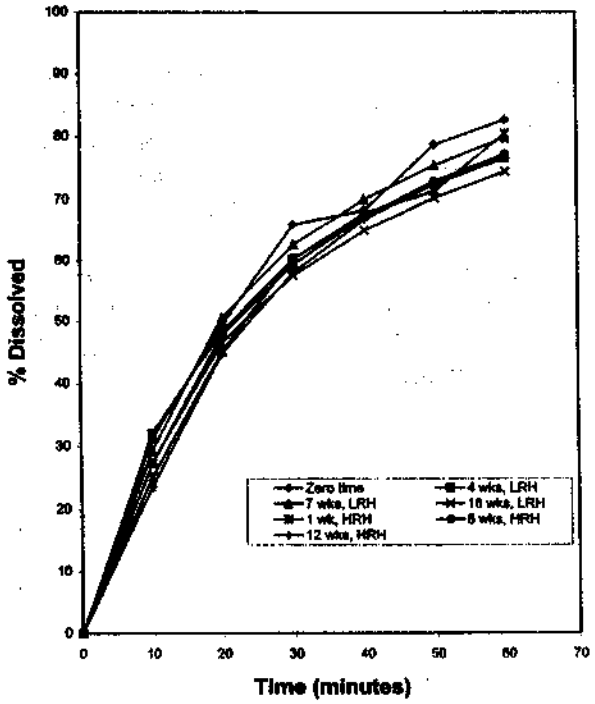

Fig. 5: Dissolution rate profiles of glibenclamide tablets using Avicel before and after storage under accelerated conditions.

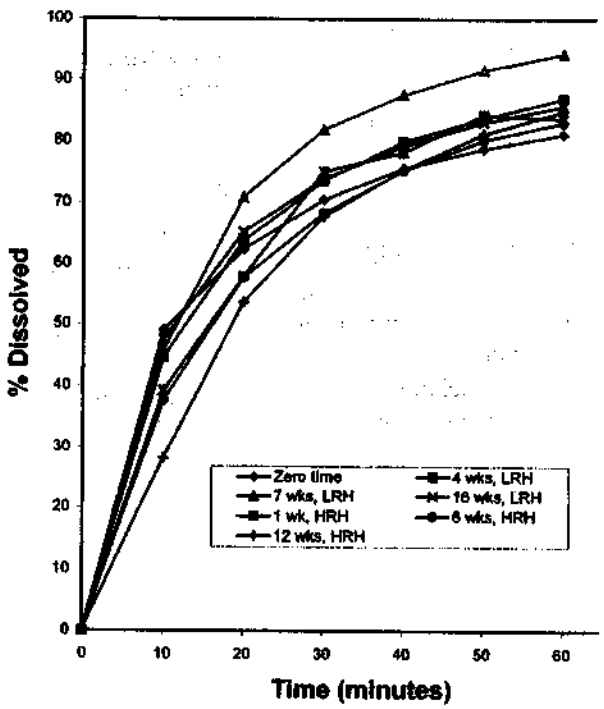

Fig. 6: Dissolution rate profiles of glibenclamide tablets using Avicel : SDL (1:3) before and after storage under accelerated conditions.

case of high RH. Under low RH conditions, however, a general increase in the dissolution was observed.

Conclusion

Cellactose did not show a superiority over the other direct compression excipients studied in all aspects of tablet properties. However, it proved to be a better vehicle than a physical mixture of its components with regard to tablet physical properties as well as in preserving tablet integrity and drug content after storage under stress condition. On the other hand, the least changes observed in the dissolution profiles of glibenclamide tablets due to storage were found for tablets made of Avicel followed by these of a mixture of Avicel : SDL (1:3) and Cellactose.

REFERENCES

1- R. F. Shangraw, in "Pharmaceutical dosage forms: Tablets", Vol. 1, eds: H. A. Lieberman, L. Lachman and J. B. Schwartz, Chapt. 4 Marcel Dekker, Inc. Publishers, 2 ed., 196 (1989).

2- P. M. Belda and J. B. Mielck, Eur. J. Pharm. Biopharm., 42, 325 (1996).

3- J. I. Wells, in "Pharmaceutical preformulation: the physicochemical properties of drug substances", Ellis Horwood Ltd., and John Willey & Sons, Publishers, Chapt. 7, 211 (1988).

4- A. Mitrevej, N. Sinchaipanid and D. Faroongsarng, Drug Dev. Ind. Pharm., 22, 587 (1996).

5- E. Doelkelr, Drug Dev. Ind. Pharm., 19, 2399 (1993).

6- M. M. C. Perales, A. Munoz-Ruiz, V. M. V. Antequera, M. N. Munoz and M. R. Jimenez-Castellanos, Drug Dev. Ind. Pharm., 22, 689 (1996).
7- C. F. Lerk, G. K. Bolhuis and A. H. deBoer, J. Pharm. Sci., 68, 205 (1979).
8- P. C. Schmidt and C. J. W. Rubensdorfer, Drug Dev. Ind. Pharm., 20, 2927 (1994).
9- G. E. Amidon and M. E. Houghton, Pharm. Res., 12, 923 (1995).
10- T. Sebhatu, A. A. Elamine and C. Ahleneck, Pharm. Res., 11, 1233 (1994).
11- R. F. Shangraw, in "Pharmaceutical dosage forms: Tablets", Vol. 1, eds: H. A. Lieberman, L. Lachman and J. B. Schwartz, Chapt. 4, Marcel Dekker, Inc. Publishers, 2 ed., 211 (1989).
12- L. Nikolic, L. J. Tasie, M. Jovanovic and Z. Djuric, Pharm. Ind., 57, 958 (1995).
13- M. S. Gordon, V. S. Rudraraju, J. K. Rhie and Z. T. Chowhan, Int. J. Pharm., 97, 119 (1993).