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# Design, Development and Evaluation of Immediate Release Gliclazide Tablets

Sanjida MAHJABEEN [1],*, Khondoker D. ALAM [2], Muhammad FAISAL [2], Nazma BEGUM [1], Farhad HOSSEN [2] & Md. R. HASSAN [2]

[1] *Department of Pharmaceutical Technology,*
[2] *Department of Clinical Pharmacy and Pharmacology,*
*Faculty of Pharmacy, University of Dhaka, Bangladesh.*

***SUMMARY*. The aim of the current study was the design, development and optimization of oral immediate release solid dosage forms of gliclazide tablets, intended for rapid action within 30 min, formulated and optimized by *in vitro* drug release method comparing with reference tablet Diamicron (Servier Lab.). For fast breakdown and rapid dissolution of tablets three different disintegrants (sodium starch glycolate, kollidone CL, and dried maize starch) were used with same percentage (2 %) in the formulations; sodium starch glycolate provide very fast release of gliclazide from tablets in pH 7.4. Two different compression methods, direct compression and wet granulation, were employed in the study. The *in vitro* drug release profile was better for directly compressed gliclazide tablets, but the flow properties of gliclazide were very poor, which causes high weight variation. Wet granulation method provided tablets of good physical parameters: two types of tablets with different hardness (8-10 kg/cm$^2$ and 5-7 kg/cm$^2$) were prepared to observe the effect of compressional forces on drug dissolution and the later one exhibits short disintegration time and rapid dissolution of gliclazide. Friability and weight variation were found within the acceptable range. Incorporation of anionic surfactant in combination with sodium starch glycolate or kollidone CL in the formulation the dissolution rate. In comparison with reference tablet, formulation containing 2 % sodium starch glycolate and 1 % sodium lauryl sulphate with other excipients as lactose, microcrystalline cellulose, povidone K-30, Mg stearate and colloidal silicon dioxide provide better dissolution. Shelf life of the formulated tablets were determined by utilizing stress condition (40 °C and 75 % Relative humidity for 3 months) and found more than 2.5 year in room condition.**

## INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike [1]. The oral route is most frequently used for introducing drugs into the body, and in fact the vast majority of drug dosage forms are designed for oral ingestion, primarily for ease of administration, it should be recognized that this mode of administration may result in inefficient and erratic drug therapy. Whenever a drug is ingested orally, one would like to have that drug absorbed into the blood stream rapidly and completely [2].

Therapeutic success of any therapy depends on the patient's compliance to ward the therapy. The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. In pharmaceutical industries, manufactures of generic tablets are usually focused on the optimization of the excipients mixture composition to obtain a product that meet established standard [3,4].

The increase in the number of generic drug products from multiple sources has placed people involved in the delivery of health care in a position of having to select one from among several seemingly equivalent products. For instance, in 1975 approximately 9 % of all prescription drugs dispensed in the United States were generic versions [5]. This figure rose to 20 % in 1984 and 40 % in 1991. Over 80 % of the approximately 10,000 prescription drugs available

*KEY WORDS:* Direct compression, Disintegration, Dissolution rate, Gliclazide, Hardness, Immediate release, Wet granulation.

* Author to whom correspondence should be addressed. *E-mail:* sanjidadup@gmail.com

in 1990 were obtained from more than one source and variable clinical responses to these dosage forms supplied by two or more drug manufacturers was documented [6]. These variable responses may be due to formulation ingredients employed, methods of handling, packaging and storage and even the rigors of in-process quality control. Thus, Odeniyi *et al.* [7] suggested that there is need to determine their pharmaceutical and therapeutic equivalence in order to ensure interchangeability. Quality control is at the heart of pharmaceuticals, one of the most tightly regulated industries across the globe. Estimates of the cost of taking a drug to market sit at the one billion mark, and much of this expense is pumped into lengthy trials and rigorous analytical tests [8]. Proving the efficacy, quality, and safety of a pharmaceutical product in order to gain 100 % confidence and approval for market is clearly a significant investment [9]. These are the reason which modulated our present study and we have chosen a generic drug to formulate and optimize in our present study.

Our Model drug is gliclazide, an oral hypoglycemic agent used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). It stimulates beta cells of the islet of Langerhans in the pancreas to release insulin. Gliclazide reduces blood glucose levels by correcting both defective insulin secretion and peripheral insulin resistance. Gliclazide increases the sensitivity of β-cells to glucose. Gliclazide also restores peripheral insulin sensitivity, such as decreasing hepatic glucose production, and increasing glucose clearance. Gliclazide has anti-platelet adhesive activity and reduces levels of free radicals, thereby preventing vascular complications. Gliclazide also has been reported to reduce plasma cholesterol and triglyceride levels after repeated administration [10].

The aim of our current project is the design, development and evaluation of oral immediate release gliclazide tablets. During the research fourteen different formulations were prepared by varying the excipients and granulation method. Those immediate release gliclazide formulations were prepared by direct compression and also wet granulation method and the dissolution profile of these formulations were individually studied in respect of physical parameters of the tablets. Four best formulations were taken and their release profile was compared to innovator product (Diamicron tablet, Servier Inc.). To induce a more holistic approach, we have studied the stability of our proposed good formulations.

## MATERIALS AND METHODS

### *Materials*

The materials used in this project were obtained from the following sources: gliclazide British Pharmacopeia grade (Zhejiang Jiuzhou Pharma Co Ltd., China); acetonitrile, magnesium stearate, methanol, potassium dihydrogen ortho phosphate, povidone K-30, sodium hydroxide pellets, sodium starch glycolate, triethylamine, trifluoroacetic acid (Merck KGaA, Germany); micro crystalline cellulose (Mingtai chemical Co Limited, Taiwan); lactose (Hilmar Ingredients, U.S.A.); sodium lauryl sulphate (Techoil Co., South Korea); Aerosil-200 (Degussa, Belgium). All other chemical and analytical reagents used were either pharmacetical or analytical grade.

### *Preparation of tablets*

Gliclazide raw material was used for the preparation of gliclazide tablet formulations F1-F14. The labeled amount of the drug substance is 80 mg per tablet. Other excipients used in formulations were micro crystalline cellulose (MCC), lactose, spray dried lactose (SDL), povidone K-30 (Pov K-30), sodium starch glycolate (SSG), sodium lauryl sulphate (SLS), magnesium stearate (Mg-st), Aerosil-200 (A-200), kollidone cross linked (Kol-CL), maize starch (DMS). The prepared gliclazide tablets were uncoated.

The immediate release tablet formulation of gliclazide (Diamicron) manufactured by Servier lab. Ltd was used as a reference product.

Formulation F1-F7 immediate release Gliclazide tablet formulations were prepared by direct compression method and F8-F 14 by wet granulation method. The tablets containing 80 mg Gliclazide were prepared by A-200 and Mg-St as lubricants; lactose and MCC were used as diluents in the total weight of 140 mg. SSG, Kol-CL and Dried Maize Starch (DMS) were used as disintegrant. Pov K-30 solution in water was used as binder to make granules in wet granulation.

For dry granulation tablets (F1-F7) the enlisted materials were mixed manually-at first gliclazide, lactose, and MCC. Then the powder was manually blended with disintegrants as Mg-St and A-200 to get the final granules. Then granules were compressed with 6 mm diameter round die-punch 140 mg. For wet granulation tablets (F8-F14) all the raw materials required for tablet preparation were weighed. Gliclazide, MCC, and DMS were mixed and sieved through Sieve No. 24. Pov K-30 solution was made in DM water and granules were prepared by adding the solution into the dry mixed powder.

Then wet mass were dried at 40 ?C in tray dryer. The dried mass was milled using Sieve No. 10 and these granules were sieved again through using Mesh No. 16. The large granules were milled & sieved again. These final granules were blended with disintegrant, SLS, Mg-St, A-200. Then the powder was compressed with 6 mm diameter round die-punch 140 mg (Table 1).

## RESULT & DISCUSSION

### *Physicochemical Characterization of Tablets*

Weight, diameter, thickness and hardness of the prepared tablets of all the formulations were checked by the standard instrumental methods complied by British Pharmacopoeia. Weight of the tablets was measured with sartorious electronic diameter and thickness was measured with a laboratory slide calipers and hardness was determined by Pfizer hardness tester. The results are given in Table 2. Each value represents average of 20 individual measurements. The disintegration time also recorded in Table 3.

### *In Vitro release study of prepared tablets*

Dissolution studies on test and reference immediate release tablets of gliclazide were conducted in USP Apparatus 2 (paddle method) with six replicates. The dissolution medium was 900 mL of phosphate buffer (pH 7.4). The paddle rotation speed was kept at 100 rpm. Dissolution media was maintained at 37 ± 1 °C. One tablet was placed in the dissolution basket. 10 ml sample were withdrawn at predetermined time intervals (every 10 min for 1 h) which were replaced immediately by 10 ml of fresh dissolution medium in order to keep original volume. After filtration by No. 1 Whatman filter paper,

| Ingredients | Dry granulation | | | | | | | Wet granulation | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) | F5 (mg) | F6 (mg) | F7 (mg) | F8 (mg) | F9 (mg) | F10 (mg) | F11 (mg) | F12 (mg) | F13 (mg) | F14 (mg) |
| Gliclazide | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 |
| MCC | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 |
| Lactose | 13.4 | 13.4 | 13.4 | 13.4 | - | - | - | 13.4 | 13.4 | 13.4 | 12 | 12 | 12 | 12 |
| Pov-K30 | - | - | - | - | - | - | - | 2.8 | 2.8 | 2.8 | 2.8 | 2.8 | 2.8 | 2.8 |
| SDL | - | - | - | - | 13.4 | 13.4 | 13.4 | - | - | - | - | - | - | - |
| SSG | 2.8 | - | - | - | 2.8 | | | 2.8 | - | 2.8 | 2.8 | - | 2.8 | - |
| Kol -CL | - | 2.8 | - | - | | 2.8 | | - | 2.8 | | - | 2.8 | - | 2.8 |
| DMS | - | - | 2.8 | | | | 2.8 | - | - | - | - | - | - | - |
| SLS | - | - | - | - | - | - | - | - | - | 1.4 | - | - | 1.4 | 1.4 |
| Mg-St | 1.12 | 1.12 | 1.12 | 1.12 | 1.12 | 1.12 | 1.12 | 1.12 | 1.12 | 1.12 | 1.12 | 1.12 | 1.12 | 1.12 |
| A-200 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 |

**Table 1**. Components of the proposed gliclazide immediate release tablets by dry granulation.

| Product code | Comp. Wt (mg) | Wt. variation (%) | Friability (%) | Diameter (mm) | Thickness (mm) | Hardness Kg/cm$^2$ |
|---|---|---|---|---|---|---|
| F1 | 140 | 15 | 1.1 | 6 | 4.65 | 4.5 |
| F2 | 140 | 8 | 1.5 | 6 | 4.70 | 5.0 |
| F3 | 140 | 16 | 1.3 | 6 | 4.68 | 5.0 |
| F4 | 140 | 15 | 0.12 | 6 | 4.70 | 4.5 |
| F5 | 140 | 8 | 0.18 | 6 | 4.9 | 4.0 |
| F6 | 140 | 17 | 0.8 | 6 | 4.78 | 5 |
| F7 | 140 | 24 | 0.7 | 6 | 4.95 | 8 |
| F8 | 140 | 5 | 0.1 | 6 | 4.7 | 10 |
| F9 | 140 | 5 | 0.14 | 6 | 4.7 | 8 |
| F10 | 140 | 4.5 | 0.21 | 6 | 4.75 | 7 |
| F11 | 140 | 4 | 0.1 | 6 | 5.1 | 5 |
| F12 | 140 | 4 | 0.08 | 6 | 5.1 | 5 |
| F13 | 140 | 3 | 0.06 | 6 | 5.1 | 5.5 |
| F14 | 140 | 3.5 | 0.08 | 6 | 5.1 | 5..5 |

**Table 2**. Physical properties of prepared immediate release Gliclazide tablets.

| Product code | Disintegration time (mean ± SD) | |
|---|---|---|
| | Time (min | BP Specification |
| F1 | 2.1 ± 0.24 | Meet |
| F2 | 2.57 ± 0.35 | Meet |
| F3 | 2.9 ± 0.41 | Meet |
| F4 | 17.96 ± 4.31 | Not meet |
| F5 | 2.94 ± 0.52 | Meet |
| F6 | 3.4 ± 0.41 | Meet |
| F7 | 3.83 ± 0.22 | Meet |
| F8 | 10.95 ± 0.44 | Meet |
| F9 | 10.58 ± 0.61 | Meet |
| F10 | 9.26 ± 0.88 | Meet |
| F11 | 6.35 ± 0.62 | Meet |
| F12 | 6.54 ± 0.95 | Meet |
| F13 | 4.20 ± 0.51 | Meet |
| F14 | 4.14 ± 0.87 | Meet |

**Table 3**. Disintegration time of the formulation F1-F14 at 37 °C and pH 7.4 phosphate buffer.

samples were assayed by UV spectrophotometer at 226 nm (Shimadzu UV-160A, Japan) against a blank of the same dissolution medium. Cumulative percentages of the drug dissolved from the tablets were calculated. Cumulative percentage drug release was calculated using an equation obtained from standard curve. The release profiles of dissolution are recorded in the Table 4 and graphically presented in Figure 1.

### *Kinetic modeling of drug release and studying the effects*

A general conclusion can be drawn that the dissolution process of immediate release gliclazide formulation tablets obeys a first-order equation. However, the process for modifed release formulation tablets proceed according to a zero-order equation [11]. Dissolution and subsequent drug release from the prepared tablets and RT (Reference Tablet-diamicron) were examined according to the standard procedure. The results obtained from the experiments were recorded in Table 4.

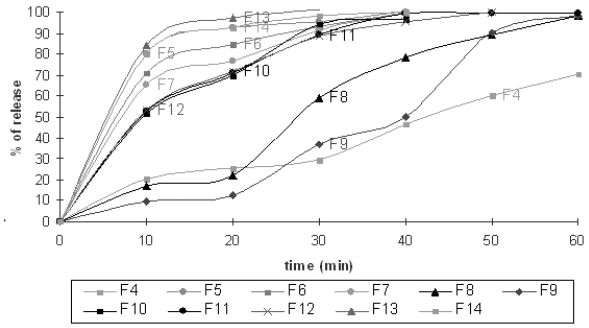


**Figure 1**. Comparative dissolution rate of formulations F4-F14.

The rate of release of drug from F11-F14 was compared with reference tablet (RT) Diamicron. It was found that F13 and F14 release the drug very quickly than diamicron. All the dissolution data were presented as mean ± SD (Table 4). Linear regression analysis of calibration curves and first-order plots were done by the least square method. Differences in the dissolution tests of all the formulation tablets were assessed by one-way analysis of variance (ANOVA). A probability *(P)* of less than 0.05 was considered statistically significant.

### *Effect of hardness on drug release from the prepared tablets*

F8 & F11 and F9 & F12 had exactly same ingredients with same percentage but they were compressed with two different compressional forces for different hardness. F8 & F9 had hard-

| Product code | Dissolution time (Percent drug release ± Standard deviation) | | | | | |
|---|---|---|---|---|---|---|
| | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min |
| F4 | 20.2 ± 3.4 | 25.4 ± 4.4 | 29.8 ± 3.1 | 36.4 ± 4.01 | 49.9 ± 4.5 | 60.5 ± 5.2 |
| F5 | 80.2 ± 2.8 | 92.6 ± 2.0 | 95.3 ± 2.2 | 100.4 ± 1.04 | | |
| F6 | 70.8 ± 1.3 | 84.9 ± 1.9 | 93.3 ± 2.5 | 99.6 ± 2.3 | | |
| F7 | 65.4 ± 1.1 | 76.5 ± 1.02 | 91.5 ± 1.6 | 99.9 ± 1.4 | | |
| F8 | 16.9 ± 4.2 | 22.0 ± 4.3 | 59.1 ± 4.1 | 78.2 ± 5.3 | 88.3 ± 4.2 | 91.3 ± 4.0 |
| F9 | 9.6 ± 3.6 | 12.4 ± 3.4 | 37.2 ± 3.0 | 50.0 ± 2.9 | 90.5 ± 2.6 | 98.3 ± 2.1 |
| F10 | 51.6 ± 2.8 | 69.7 ± 3.1 | 74.4 ± 2.9 | 86.4 ± 2.9 | 91.4 ± 2.1 | 99.5 ± 1.9 |
| F11 | 52.6 ± 2.9 | 70.8 ± 3.5 | 89.5 ± 2.4 | 99.7 ± 2.1 | 99.54 ± 2.1 | 99.7 ± 1.1 |
| F12 | 53.7 ± 2.1 | 71.4 ± 1.2 | 88.6 ± 1.0 | 95.3 ± 0.87 | 100 ± 0.9 | |
| F13 | 84.2 ± 1.1 | 97.3 ± 1.0 | 101.4 ± 0.7 | | | |
| F14 | 80.2 ± 2.0 | 92.4 ± 2.1 | 98.1 ± 1.9 | 100.3 ± 1.2 | | |
| RT | 68.2 ± 3.2 | 84.3 ± 1.6 | 95.6 ± 1.1 | 98.7 ± 1.13 | 99.9 ± 1.4 | 100.4 ± 1.1 |

**Table 4**. Dissolution time of the formulation F4-F14 at 37 °C and pH 7.4 phosphate buffer.

ness value 8-10 kg/cm² and F11 & F12 had 5-7 kg/cm². After dissolution study it shows that F11 and F12 exhibit better drug release from the tablet *in vitro* (Fig. 1).

### *Effect of surfactant on drug release from the prepared tablets*

An anionic surfactant Sodium lauryl sulphate was incorporated in formulation F13 with sodium starch glycolate 2 % and in the formulation F14 with kollidone CL 2 %. Then dissolution rate were measured and found that surfactant markedly increase the dissolution rate (Fig. 1).

### *Effect of lubricant on drug release from the prepared tablets*

F11 contains hydrophobic lubricant Magnesium Stearate and F13 contains hydrophilic lubricant sodium lauryl sulphate. After dissolution study it shows that hydrophilic lubricant causes rapid drug release from tablet (Fig. 1).

### *Effect of manufacturing process (compression method) on dissolution rate*

F5, F6, F7 were prepared by direct compression method and F8, F9, F10 were prepared by wet granulation method keeping the same ingredients and found that tablets made by direct compression offer good dissolution profile (Fig. 1).

### *Accelerated Stability Testing of Formulations F11-F14*

Tablets of F11, F12, F13 and F14 were blistered by aluminium-PVC foil, packed in swedish board paper carton (350 GSM) and kept in stability chamber to subject a stress condition of 40 °C/75 % RH (Relative Humidity) for 3 months and assay tests were done in every month. The physical parameters were acceptable. Dissolution studies were also performed for F11-F14 and the results were recorded in Table 5.

### *Determination of Rate Constant and Shelf Life for Formulations F11-F14*

The purpose of the stability study is to provide evidence on how the quality of a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish the shelf life for the drug product and the recommended storage conditions [12]. In present study we have used 3 months stability data in accelerated condition to estimate the shelf life (Table 6).

In the pharmaceutical field, the time required for 10 % of the drug to degrade is an important value to know, since it represent a reasonable limit of degradation of active ingradients. The $t_{10}$ % value can be calculated as follows [13]:

$$t_{10\,\%} = \frac{2.303}{k} \log \frac{100}{90} = \frac{0.104}{k}$$

where $k$ = first order rate constant [14], and $t_{10\,\%}$ = shelf life. The estimated shelf life was stated in Table 6.

| Product code | Percent drug release ± Standard deviation | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 min | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min |
| F11 | 0 | 51.85 | 69.98 | 88.86 | 98.23 | 98.56 | 99.68 |
| F12 | 0 | 52.46 | 71.02 | 86.9 | 94.17 | 98.35 | 99.42 |
| F13 | 0 | 84.01 | 96.59 | 99.06 | -- | -- | -- |
| F14 | 0 | 80.24 | 90.35 | 95.64 | 98.67 | 99.62 | -- |

**Table 5**. Dissolution study of the formulation F11-F14 after 3 month (Study condition: 40 °C/75 % RH).

| Sample code | Initial | Content of Gliclazide per tab (mg) | | | Remarks regarding official specification | Rate Constant (K) $h^{-1}$ | Shelf life at room temp. (day) |
|---|---|---|---|---|---|---|---|
| | | After 1 month | After 2 months | After 3 months | | | |
| F11 | 79.95 | 79.58 | 79.02 | 78.85 | OK | $1.539 \times 10^{-4}$ | 675.49 |
| F12 | 81.06 | 80.28 | 80.09 | 79.94 | OK | $1.546 \times 10^{-4}$ | 672.62 |
| F13 | 80.45 | 80.16 | 80.02 | 79.68 | OK | $1.068 \times 10^{-4}$ | 973.07 |
| F14 | 79.25 | 79.05 | 78.96 | 78.47 | OK | $1.099 \times 10^{-4}$ | 946.14 |

**Table 6**. Determination of quantity of the formulation F11-F14 after stress testing and estimated shelf life.

## CONCLUSIONS

The aim of this study was to prepare a high quality formulation of gliclazide tablets in terms of disintegration time and dissolution profiles. Among the fourteen formulations, granules of the entire batch meet assay parameter that means powders or granules were properly mixed. F1-F14 comply BP specification in terms of assay. F1-F7 produced by direct compression method fails in weight variation, they show very high weight variation that exceed the limit, but F8-F14 compressed by wet granulation method show very good result in terms of weight variation, tablet hardness, thickness, friability etc. all the physical parameters and also assay.

To investigate the reasons behind this behavior of formulation some possible causes can be predicted as: (1) bad flow property of active Gliclazide raw materials, (2) insufficient quantity of granules in the powder mix to make good flow in direct compression formula, and (3) added excipients do not provide sufficient flow of powder in F1- F7.

The possible reason for good flow of F8- F14 may be attributed to incorporation of binder solution to powder mix. After drying as the granules were same sized because of seiving through 20 mesh screen, and there was a mixture of powder and granules they show good flow.

From this study, we see if raw materials have poor flow property or if it make problem with direct compression e.g. for high weight variation, high friability, low hardness etc. then wet granulation is preferable than direct compression. High weight variation in drug products is absolutely unexpected, dangerous and not permissible under any circumstance although it meet the assay and dissolution parameter. If the tablet weight is higher than limit, it contain high amount of drug that cause toxicity in our body after administration. Drug products are quite different from other types of consumer products as the former ones are used to prevent or cure diseases and to improve health conditions. Thus there should be no compromise regarding their quality. So, although having good disintegration, dissolution and assay result, some formulations were discarded.

Dissolution profiles of these formulas were compared with a reference tablet. The rate of releases of drug from F11 –F14 were compared with reference tablet (RT) Diamicron (Fig. 2). It was found that F13 and F14 release the drug

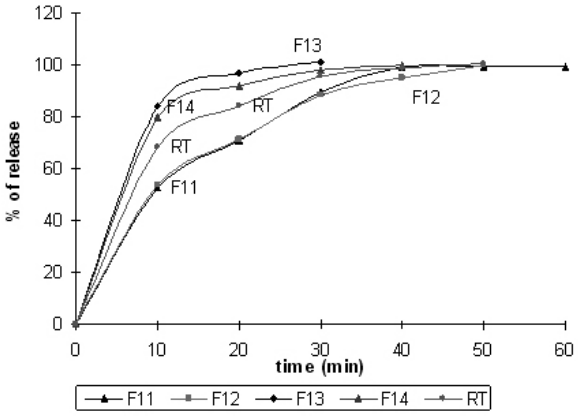


**Figure 2**. Dissolution rate of RT (reference tablet) Diamicron with four good formulations F11- F14.

quicker than Diamicron. In this study, the effect of hardness of tablet was observed on disintegration time and dissolution rate. The study showed that high hardness or high compression force make a comparatively harder tablet with slow dissolution. From Fig. 1, it is clearly revealed that hydrophilic lubricant causes quick drug release from the tablet along with its lubricant effect.

From this study it can also be noted that addition of surfactant on the tablet formulation causes a marked increase in dissolution rate and drugs are release from the tablet within a short time. Here the formulation F13 and F14 offer very good result in dissolution compared to reference tablet. Table of stability testing (Table 6) implies that all four formulas F11-F14 meet BP specification for assay and dissolution study but in case of shelf life determination F13 and F14 offers the best result.

For accelerated stability study of a drug product, it should be studied in different temperature range e.g. 45 °C, 60 °C, 85 °C temperatures. But in this study due to unavailability of stability chamber, stability was only checked at 40 °C temperature with 75 % relative humidity.

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