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## PHARMACEUTICAL TECHNOLOGY

# FORMULATION AND EVALUATION OF METFORMIN ORO-DISPERSIBLE TABLETS

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**Abstract:** The purpose of this research was to develop oro-dispersible tablets of metformin by direct compression method using super disintegrants approach, effervescent approach and sublimation approach. Powder blend was evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and bulkiness. The tablets were evaluated for uniformity of weight, friability test, hardness, drug content, wetting time, water absorption ratio, disintegration time and *in vitro* dissolution. Higher dissolution rates were achieved in selected batches (A5, B4, C4, and D3) as compared to marketed product. Batch C4 prepared by effervescent approach was found to have the least disintegration time and maximum *in vitro* dissolution profile.

**Keywords:** oro-dispersible tablets, metformin, superdisintegrating agents, effervescent agents, sublimation agents

Tablets are the most widely used dosage form because of its convenience in terms of self-administration, compactness and easy manufacturing. However, geriatric and pediatric patients have difficulty in swallowing. Almost 50% of the population is affected by such problem resulting in the high incidence of non compliance and ineffective therapy (1). Most of pharmaceutical dosage forms for oral administration are formulated for direct ingestion or for chewing or for prior dispersion and dissolution in water and some of them are absorbed in the mouth (sublingual or buccal tablets). To obviate the problems associated with conventional dosage forms, oro-dispersible tablets have been developed (2). A solid dosage form that dissolves or disintegrates rapidly in oral cavity resulting in solution or suspension without the need of water is known as oro-dispersible or fast dispersing tablets. Oro-dispersible tablets disintegrate or dissolve rapidly in the saliva without the need of water. When an oro-dispersible tablet is placed in the mouth saliva causes it to dissolve rapidly (usually within 60 s) and to disperse the dosage form so that the saliva contains the dissolved or dispersed medicament. The patient then swallows the saliva-medicament mixture (in liquid form) and it reaches the stomach. From there, the active pharmaceutical ingredient (API) is absorbed into the blood stream. For some API, portion of the medicament is also absorbed through the mouth, pharynx and esophagus as the medicament-saliva mixture descends into the stomach. In this way, oro-dispersible tablets provide a rapid onset of action and prevent hepatic first-pass metabolism. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form (3). The oro-dispersible tablets can be prepared by the addition of superdisintegrants, effervescent approach and sublimation technique. A number of superdisintegrants such as crosscarmellose sodium, crosspovidone, sodium starch glycolate act by swelling, wicking and capillary action and causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration (4). The effervescent system is generally composed of a dry acid and dry base which, when react, facilitate a mild effer-

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vescent reaction when the tablet contacts saliva. The effervescent reaction accelerates the disintegration of tablet through the release of carbon dioxide, water and salt. Due to evolution of carbon dioxide the bitter taste of drug is also masked and pleasant mouth feel is felt (5). The volatile materials like urea, ammonium carbonate, ammonium bicarbonate, and camphor can be compressed into tablets using the conventional method and further they can be removed *via* sublimation, resulting in highly porous structures, and as a result tablet disintegrates within seconds (6).

Table 1. Formulation of batches A1–A6.

| Ingredients | A1 | A2 | A3 | A4 | A5 | A6 |
|---|---|---|---|---|---|---|
| Metformin | 500 | 500 | 500 | 500 | 500 | 500 |
| Sodium starch glycolate | 65 | 72 | 80 | 85 | 91 | 98 |
| Mannitol | 15 | 18 | 21 | 23 | 26 | 29 |
| Microcrystalline cellulose | 55 | 45 | 34 | 27 | 18 | 08 |
| Aspartame | 10 | 10 | 10 | 10 | 10 | 104 |
| Magnesium stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Talc | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Total weight | 650 | 650 | 650 | 650 | 650 | 650 |

All quantities are expressed in mg.

Table 2. Formulation of batches B1–B6 and C1–C6.

| Ingredients | B1 | B2 | B3 | B4 | B5 | B6 | C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metformin | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| Citric acid | 30 | 32 | 35 | 37 | 40 | 42 | 30 | 32 | 35 | 37 | 40 | 42 |
| Sodium bicarbonate | 30 | 36 | 42 | 48 | 60 | 63 | 30 | 36 | 42 | 48 | 60 | 63 |
| Sodium starch glycolate | – | – | – | – | – | – | 65 | 57 | 48 | 40 | 25 | 20 |
| Glycine powder | 65 | 57 | 48 | 40 | 25 | 20 | – | – | – | – | – | – |
| Aspartame | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Total weight | 650 | 650 | 650 | 650 | 650 | 650 | 650 | 650 | 650 | 650 | 650 | 650 |

All quantities are expressed in mg.

Table 3. Formulation of batches D1–D3 and E1–E3.

| Ingredients | D1 | D2 | D3 | E1 | E2 | E3 |
|---|---|---|---|---|---|---|
| Metformin | 500 | 500 | 500 | 500 | 500 | 500 |
| Ammonium bicarbonate | 60 | 70 | 80 | – | – | – |
| Camphor | – | – | – | 60 | 70 | 80 |
| Mannitol | 50 | 40 | 30 | 50 | 40 | 30 |
| Sodium starch glycolate | 30 | 30 | 30 | 30 | 30 | 30 |
| Aspartame | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium Stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Talc | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Total weight | 650 | 650 | 650 | 650 | 650 | 650 |

All quantities are expressed in mg.

Metformin hydrochloride is an orally administered antihyperglycemic agent used in the management of non-insulin dependent (type-2) diabetes mellitus. Metformin is chemically 3-(diaminomethylidene)-1,1-dimethylguanidine. Metformin improves glycemic control by improving insulin sensitivity and decreasing intestinal absorption of glucose (7). In the present study, oro-dispersible tablets of metformin HCl were formulated by various approaches to achieve rapid onset of action and improved bioavailability.

## EXPERIMENTAL

### Materials

Metformin HCl was obtained as a gift sample from Comed Pharmaceutical Pvt. Ltd., Vadodara India. Sodium starch glycolate and microcrystalline cellulose were obtained from Leo Chem Pharmaceutical Pvt. Ltd., India. Mannitol was obtained from Qualigens Fine Chemicals Pharmaceutical Pvt. Ltd. (Mumbai). Sodium bicarbonate and ammonium bicarbonate were obtained from Merck Pharmaceutical Pvt. Ltd., India and Camphor was obtained from Fisher Pharmaceutical Pvt. Ltd., India.

### Direct compression

Specified quantities of different ingredients used in different formulation batches (A1-A6, B1-B6, C1-C6, D1-D3, E1-E3) were weighed and passed through sieve #60 and co-grounded to get powder blend. The powder blend was further evaluated in terms of angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and bulkiness (to check its flow property) and compressibility index. Then, powder blends of different batches were compressed using tablet punching machine to get oval shaped tablets.

Batches A1-A6 were prepared using sodium starch glycolate (10–15% w/w) *via* superdisintegrant approach. Batches B1-B6 were prepared using citric acid and sodium bicarbonate (1:1–1:1.5% w/w) and batches C1–C6 were prepared using citric acid and sodium bicarbonate (1:1–1:1.5% w/w) and sodium starch glycolate (3–10% w/w) *via* effervescent approach. Batches D1–D3 were prepared using ammonium bicarbonate (9–12% w/w) and batches E1-E3 were prepared using camphor (9–12% w/w) *via* sublimation approach. Composition of all batches using different approaches is shown in Tables 1–3.

### Evaluation of pre-compression parameters

### Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is determined by the funnel method. Angle of repose less than $30^{o}$ shows the free flowing of the material (8). Angle of repose was determined by the following formula:

$$\text{Angle of repose} = \tan \Phi \times 2h/D$$

where d is the diameter of pile and h is the height of pile.

### Bulk density

Bulk density is defined as the mass of the powder divided by the bulk volume (9) and is expressed as $g/cm^3$:

$$\text{Bulk density} = \text{mass of powder} / \text{bulk volume of powder}$$

### Tapped density

Blend was taken and filled in 10 mL measuring cylinder which was tapped until the constant height was obtained (10).

$$\text{Tapped density} = \text{mass of powder} / \text{volume of powder after tapping}$$

### Compressibility index

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow. It is given by % compressibility and calculated as (11):

$$C = (t-b)/t \times 100$$

where t is the tapped density and b is the untapped bulk density.

### Hausner's ratio

Hausner's ratio is an index of ease of powder flow and is calculated by following formula (12):

$$\text{Hausner's ratio} = t/b$$

where t denotes tapped density and b denotes untapped bulk density.

### Bulkiness

Specific bulk volume or reciprocal of bulk density is called as bulkiness or bulk. The bulkiness was calculated by the following formula (13):

$$\text{Bulkiness} = 1/b$$

where, b is the bulk density.

### Evaluation of tablets

Uniformity of weight

Twenty randomly selected tablets were weighed individually and the average weight was calculated (14).

Tablet hardness

Hardness of the tablets was measured using Monsanto hardness tester (15).

Table 4. Precompression parameters of all batches (A1–A6, B1–B6, C1–C6, D1–D3 and E1–E3).

| Formulation code | Angle of repose ($^o$) | Bulk density (g/cm$^3$) | Tapped density (g/cm$^3$) | Compressibility index | Hausner's ratio | Bulkiness |
|---|---|---|---|---|---|---|
| A1 | 27.32 | 0.55 | 0.63 | 12.6 | 1.14 | 1.81 |
| A2 | 28.01 | 0.53 | 0.62 | 14.5 | 1.16 | 1.88 |
| A3 | 28.73 | 0.55 | 0.67 | 17.9 | 1.21 | 1.81 |
| A4 | 28.20 | 0.52 | 0.61 | 14.7 | 1.17 | 1.92 |
| A5 | 29.30 | 0.59 | 0.68 | 13.0 | 1.15 | 1.69 |
| A6 | 27.65 | 0.53 | 0.60 | 11.6 | 1.13 | 1.88 |
| B1 | 28.22 | 0.57 | 0.65 | 12.3 | 1.14 | 1.75 |
| B2 | 29.31 | 0.51 | 0.59 | 13.5 | 1.15 | 1.96 |
| B3 | 30.37 | 0.53 | 0.62 | 14.5 | 1.16 | 1.88 |
| B4 | 27.20 | 0.58 | 0.69 | 15.9 | 1.18 | 1.72 |
| B5 | 28.10 | 0.52 | 0.61 | 14.7 | 1.17 | 1.92 |
| B6 | 27.55 | 0.54 | 0.61 | 11.4 | 1.12 | 1.85 |
| C1 | 29.32 | 0.55 | 0.64 | 14.0 | 1.16 | 1.81 |
| C2 | 27.42 | 0.51 | 0.62 | 17.7 | 1.21 | 1.21 |
| C3 | 28.21 | 0.54 | 0.63 | 14.2 | 1.16 | 1.85 |
| C4 | 25.19 | 0.59 | 0.67 | 11.9 | 1.13 | 1.69 |
| C5 | 27.20 | 0.53 | 0.60 | 11.6 | 1.13 | 1.80 |
| C6 | 29.45 | 0.52 | 0.61 | 14.7 | 1.17 | 1.92 |
| D1 | 28.22 | 0.57 | 0.65 | 12.3 | 1.14 | 1.75 |
| D2 | 29.51 | 0.51 | 0.60 | 15.0 | 1.17 | 1.96 |
| D3 | 27.32 | 0.59 | 0.65 | 13.0 | 1.15 | 1.69 |
| E1 | 26.31 | 0.53 | 0.62 | 14.5 | 1.16 | 1.88 |
| E2 | 29.41 | 0.54 | 0.63 | 14.2 | 1.16 | 1.85 |
| E3 | 28.35 | 0.52 | 0.61 | 14.7 | 1.17 | 1.92 |

Friability test

Friability of the tablets was determined using Almicro Friabilator at 25 rpm for 4 min. Twenty tablets were weighed and loss in weight (%) was calculated (16).

Drug content

Twenty tablets were weighed and powdered. Weighed accurately a quantity of the powder containing 0.1 g metformin hydrochloride was shaked with 70 mL of water for 15 min, diluted to 100 mL with water and filtered. Further dilutions were made and absorbance of resulting solution was determined at 236 nm (14).

Wetting time

A glass Petri dish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was noted as wetting time (17).

Water absorption ratio

A piece of tissue paper was folded twice and placed in a small Petri dish containing 6 mL of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed (18). Water absorption ratio R, was determined using the following equation:

$$R = 100 \times W_a – W_b/W_b$$

where $W_b$ is the weight of tablet before water absorption and $W_a$ is the weight of tablet after water absorption.

Disintegration time

The time required for disintegration of six tablets, placed in each tube of disintegration test apparatus (USP) was measured at 37 ± 2$^o$C using 900 mL of distilled water (19).

Dissolution testing

*In vitro* dissolution study of metformin tablets was performed using phosphate buffer (pH 6.8) maintained at a temperature of 37 ± 0.5°C in USP II dissolution test apparatus and at rotation speed of 50 rpm. At a predetermined time interval (5, 10, 15, 20, 30, 45 and 60 min), samples were withdrawn and filtered through Whatman filter paper. Absorbance of suitably diluted samples was determined by UV spectrophotometer at 236 nm and the percentage of drug release was calculated. The dissolution experiments were conducted in triplicate (20).

## RESULTS AND DISCUSSION

### Evaluation of pre-compression parameters:

All the batches showed the value of angle of repose ranged from 26° to 30° indicating good flow properties. The compressibility of powder mixture was within the range of 11–15 indicating that all the formulations showed good compressibility. Bulkiness was found to be in the range of 1–2 as shown in Table 4.

### Evaluation of tablets

Disintegration time of batches A1–A6 was in the range of 17.8–44.1 s. As the amount of SSG (Batch A1–A6, 10–14%) increases up to certain amount, the wetting time and disintegration time decreases. Further increase in SSG lead to an increase in wetting time and disintegration time (Batch A6). Batch A5 was selected for further dissolution studies as disintegration time (17.8 s) and wetting time (5.1 s) was lower in comparison to other batches.

Disintegration time of batches B1–B6 was in the range of 15.3–44.5 s. As the amount of citric

Table 5. Physical parameters of all batches (A1–A6, B1–B6, C1–C6, D1–D3 and E1–E3).

| Code | Weight variation (mg) | Hardness (kg/cm$^2$) | Friability (%) | Drug content (%) | Wetting time (s) | Water absorption ratio (%) | Disintegration time (s) |
|---|---|---|---|---|---|---|---|
| A1 | 649.6 ± 2.2 | 3.01 | 0.30 | 99.1 | 7.1 ± 0.15 | 1.3 | 44.1 ± 2.04 |
| A2 | 649.86 ± 2.6 | 3.13 | 0.28 | 99.5 | 6.9 ± 0.1 | 1.5 | 38.5 ± 1.4 |
| A3 | 649 ± 2.2 | 3.46 | 0.26 | 98.8 | 6.0 ± 0.25 | 0.53 | 28.5± 1.6 |
| A4 | 648.9 ± 2.7 | 3.89 | 0.34 | 99.7 | 5.9 ± 0.11 | 0.66 | 20.8 ± 1.1 |
| A5 | 651 ± 3.8 | 3.11 | 0.27 | 99.1 | 5.1 ± 0.1 | 1.0 | 17.8 ± 1.1 |
| A6 | 649.1 ± 4.7 | 3.08 | 0.26 | 99.9 | 5.9 ± 0.5 | 1.2 | 21.8 ± 1.4 |
| B1 | 649.1 ± 4.7 | 2.8 | 0.32 | 98.6 | 7.1 ± 0.13 | 1.2 | 44.5 ± 1.04 |
| B2 | 649.6 ± 2.1 | 3.1 | 0.29 | 99.9 | 6.7 ± 0.27 | 1.9 | 32.9 ± 1.7 |
| B3 | 648 ± 1.47 | 3.5 | 0.23 | 99.1 | 5.9 ± 0.21 | 0.51 | 23.7 ± 1.6 |
| B4 | 650.3 ± 2.9 | 3.7 | 0.20 | 98.9 | 5.1 ± 0.12 | 0.55 | 15.3 ± 1.4 |
| B5 | 651 ± 3.5 | 2.9 | 0.31 | 99.1 | 5.6 ± 0.17 | 1.7 | 20.1 ± 1.3 |
| B6 | 649.5 ± 4.1 | 3.0 | 0.28 | 98.7 | 5.9 ± 0.5 | 1.1 | 22.8 ± 1.1 |
| C1 | 648.6 ± 2.1 | 2.71 | 0.31 | 99.7 | 7.0 ± 0.25 | 1.1 | 36.1 ± 1.04 |
| C2 | 649 ± 2.7 | 2.94 | 0.30 | 99.1 | 6.8 ± 0.21 | 0.54 | 30.3 ± 1.1 |
| C3 | 649.8 ± 1.2 | 3.71 | 0.23 | 98.3 | 5.3 ± 0.15 | 0.61 | 22.7 ± 1.3 |
| C4 | 652.1 ± 2.3 | 3.59 | 0.26 | 97.9 | 4.8 ± 0.17 | 1.2 | 12.9 ± 1.9 |
| C5 | 650 ± 3.8 | 2.9 | 0.35 | 98.9 | 5.0 ± 0.14 | 0.89 | 14.7 ± 1.3 |
| C6 | 649 ± 4.1 | 3.09 | 0.25 | 99.5 | 6.0 ± 0.43 | 1.1 | 22.3 ± 1.1 |
| D1 | 649 ± 2.1 | 3.23 | 0.28 | 100.1 | 7.2 ± 0.25 | 1.5 | 38.1 ± 2.1 |
| D2 | 648.86 ± 2.9 | 3.01 | 0.31 | 99.9 | 6.1 ± 0.17 | 1.7 | 27.9 ± 1.5 |
| D3 | 649.7 ± 1.9 | 3.51 | 0.21 | 99.3 | 5.0 ± 0.15 | 0.98 | 18.1 ± 1.1 |
| E1 | 650.3 ± 2.3 | 3.60 | 0.18 | 98.97 | 5.3 ± 0.21 | 1.77 | 40.0 ± 1.9 |
| E2 | 650 ± 2.8 | 3.07 | 0.25 | 100.5 | 5.9 ± 0.11 | 0.88 | 26.4 ± 1.1 |
| E3 | 649.4 ± 3.7 | 2.90 | 0.35 | 99.7 | 6.0 ± 0.7 | 1.4 | 19.4 ± 2.4 |

± indicates standard deviation.

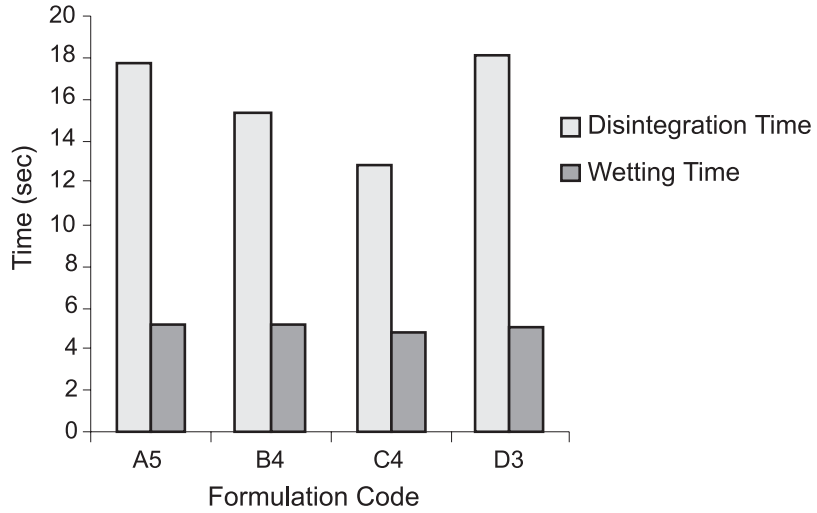


Figure 1. Comparison of disintegration time and wetting time of selected batches of metformin oro-dispersible tablets

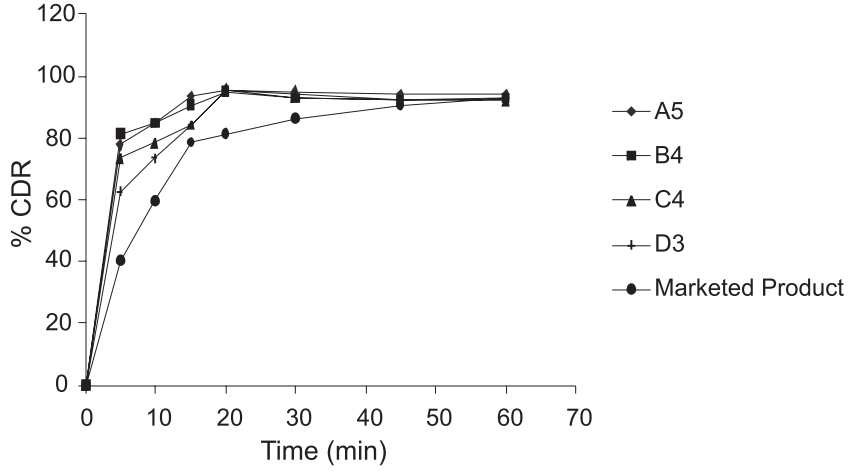


Figure 2. *In vitro* dissolution profile of selected batches and marketed product

acid and sodium bicarbonate increases, the wetting time and disintegration time decreases (Batches B1-B4). However, the wetting time and disintegration time increases with further increase in citric acid and sodium bicarbonate (Batch B5 and B6). Batch B4 was selected for further dissolution studies as disintegration time (15.3 s) and wetting time (5.1 s) was lower in comparison to other batches.

Disintegration time of batches C1–C6 was in the range of 12.9–36.1 s. As the amount of citric acid, sodium bicarbonate and SSG increases, the wetting time and disintegration time decreases (Batch C1–C4), whereas further increase lead to increased wetting time and disintegration time (Batch C5 and C6). Batch C4 was selected for further dissolution studies as disintegration time (12.9 s) and wetting time (4.8 s) was lower in comparison to other batches.

Disintegration time of batches D1–D3 and E1–E3 was in the range of 18.1–40.1 s. As the amount of ammonium bicarbonate and camphor (Batch D1–D3 and E1–E3) increases, the wetting

time and disintegration time decreases. Batch D3 was selected for further dissolution studies as disintegration time (18.1 s) and wetting time (5.0 s) was lower in comparison to other batches.

Table 5 shows physical parameters of all the batches. The batches passed the weight variation test as acceptance criteria. Hardness of the batches was in the range of 2–4 kg/cm$^2$. The friability of the batches was within acceptable limits (less than 1%) and wetting time was found to be 5–7 s. The selected batches from different approaches (A5, B4, C4 and D3) were compared based on their disintegration time and wetting time data (Fig. 1). It has been found that batch C4 showed the least disintegration time (12.9 s) and wetting time (4.8 s).

### *In vitro* dissolution test

*In vitro* release of the selected batches A5, B4, C4, D3 was determined using USP II apparatus and compared with that of marketed product (Fig. 2). The extent of drug release after 60 min was almost the same in case of different batches and marketed product. Higher extent of drug release (95%) was observed in 20 min in selected formulation batches as compared to that of marketed product (81%), which indicates higher dissolution rate in selected formulation batches (Fig. 2). It supports rapid onset of action in formulation batches. Batch A5 has showed improved dissolution profile in comparison to all the batches, whereas batch C4 showed the lowest disintegration time.

## CONCLUSION

The oro-dispersible tablets of metformin were successfully prepared by direct compression method using the addition of superdisintegrants or effervescent approach or sublimation technique. Out of these different formulations, batch A5 has shown improved dissolution profile and batch C4 showed the lowest disintegration time in comparison to all other batches. Therefore, the batches A5 and C4 are highly promising in improving the disintegration and dissolution characteristics and thereby enhancing the bioavailability of metformin.

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