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CORRELATION BETWEEN BASKET AND PADDLE DISSOLUTION TEST METHODS BY DRUG RELEASE IN SOLID DOSAGE FORMS FROM NIZATIDINE AND RAMIPRIL

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ABSTRACT

Dissolutions studies used both paddle and basket methods to carry to cumulative percent of drug release. In both apparatus which one performs good drug releasing characteristics and simplicity? Pharmaceutical companies strive to ensure that the drugs they product are manufactured in a way that they get absorbed at a rate that will ensure optimum effectiveness of the drug in the body. The rotating speed of the shaft and temperature of the liquid in the vessel is precisely controlled to stomach. The time taken to fully dissolve to sample is then recorded for the scientific analysis. The paddle dissolution method and basket dissolution methods however have unique differences in the way they are carried out. In both methods same conditions are maintained but difference only basket instead of paddle in the equipment. The cumulative perentage of controlled drug release in both methods was very slight difference. Above research studies they are confirm to use in Nizatidine and Ramipril matrix tablets, the percentage of drug release was very slight difference and correlated.

INTRODUCTION

MATERIALS AND METHODS

Nizatidine: Nizatidine was Kind gift sample from Hetero Pharma India Pvt Ltd, Hyderabad, India. HPMC K4M, Guargum, Carbapol-934 from KP labs, Talc and Magnesium stearate were procured from saraswathia Chemie Pvt Ltd; Mumbai, India. Lactose, PolyvinylPyrollidone and Isopropyl alcohol were procured from S.d fine chem. Pvt Ltd; Mumbai, India. All other chemicals and reagents used were of analytical grade.

Ramipril: Ramipril was kind gift sample from yarrow chemicals private limited, Mumbai India. HPMCK15M, Talc, and Magnesium stearate were procured from KP labs, Hyderabad, India.

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Lactose, Karayagum, Isopropyl alcohol, Polyvinyl pyrrolidone were procured from S.d fine chemicals Pvt Ltd; Mumbai, India. All other chemicals and reagents were used of analytical grade.

Preparation of CR tablets

Nizatidine

Six formulations of controlled release tablets of nizatidine using HPMC K4M and Guargum with three ratios (1:1, 1:2, 1:3) were prepared by wet granulation method. Nizatidine and polymers were mixed separately. Lactose were added to the drug polymer mixture and blended thoroughly for 5 minutes. PolyvinylPyrollidone (PVP) was dissolved in sufficient quantity of isopropyl alcohol (IPA) until it forms a solution and this was added to the drug mixture and mixed thoroughly to form a coherent mass [15]. Then the coherent mass was passed through Sieve No: 16 to form granules and the collected granules were dried at 40°C±2°C for 2 hours. The dried granules were passed through sieve No: 22. The granules retained on sieve No: 22 were evaluated for bulk density,

tapped density; bulkiness, angle of repose (Hadjiioannou, 1993), compressibility index and Hausener's ratio (Table-II&III). Then the granules were mixed with magnesium stearate, talc and finally compressed into tablets (Siepmann, 2001).

Ramipril

Six formulations of controlled release tablets of Ramipril using HPMCK15 and karaya gum each with four formulations (1:1, 1:2, and1:3) were prepared by wet granulation method (Chivate, 2008). The details of each formulation and with composition are shown to Table-2. Ramipril (drug) and polymers HPMCK15M, Karayagum were mixed separately. Lactose and cross caramellose sodium were added to the polymer-drug mixture and blended thoroughly for 5-6 minutes. A coherent mass is formed to dissolve the polyvinyl pyrrolidone (PVP) in sufficient quantity of isopropyl alcohol (IPA) and finally added to drug mixture (Chirico, 2007). Then the coherent mass was passed through sieve number-16 to form granules and the collected granules were dried at $40°C \pm 2°c$ for 2 hours. The dried granules were passed through the sieve number-22.The granules retained on sieve number-22 were evaluated for tapped density, bulk density, bulkiness, compressibility index, Hausners index [4] and angle of repose. Then the granules were mixed with talc, magnesium stearate and finally compressed in to tablets (Chein, 1992).

Table 3. Composition of matrix tablet formulation of Nizatidine

Ratio's of Drug and polymer	Nizatidine: HPMCK4M			Nizatidine: Guargum		
Ingredients(mg)	A1	A2	A3	B1	B2	B3
Nizatidine	10	10	10	10	10	10
HPMCK4M	10	20	30			
Guargum				10	20	30
Eudragit	5	5	5	5	5	5
Lactosemonohydrade	61	51	41	61	51	41
Magnesium state	6	6	6	6	6	6
Talc	8	8	8	8	8	8
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
Total	100	100	100	100	100	100

Table 4. Composition of matrix tablet [7] formulation of Ramipril

Ratio's of Drug and polymer	Ramipril: HPMCK15M			Ramipril: Karayagum		
Ingredients(mg)	C1	C2	C3	D1	D2	D3
Ramipril	10	10	10	10	10	10
HPMCK15M	10	20	30			
Karayagum				10	20	30
Lactosemonohydrade	65	55	45	65	55	45
Cross caramellose sodium	5	5	5	5	5	5
Magnesium state	4	4	4	4	4	4
Talc	6	6	6	6	6	6
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
Total	100	100	100	100	100	100

Tapped density was within the range of 0.49 to 0.52 gm/cm^3. Bulkiness was found to be the range of 2.36 to 2.46 gm/cm^3.

Table 3. Evaluation of Nizatidine Granules (F1 to F65)

Parameters	A1	A2	A3	B1	B2	B3
Bulk density(gm/cm³)*	0.46±0.11	0.43±0.11	0.41±0.31	0.45±0.22	0.43±0.18	0.45±0.16
Tapped density(gm/cm³)	0.52±0.63	0.49±0.24	0.45±0.13	0.51±0.81	0.49±0.17	0.49±0.26
Bulkiness(gm/cm³)*	2.36±0.91	2.41±0.39	2.46±0.13	2.39±0.11	2.41±0.18	2.44±0.11
Angle of repose*	29.61±0.29	28.63±0.35	28.01±0.29	29.05±0.06	28.59±0.63	28.05±0.06
Compressibility index*	13.06±0.0.39	12.89±0.21	12.26±0.17	13.36±0.15	12.87±0.11	13.23±0.10
Hausener's index*	1.17±0.26	1.16±0.79	1.15±0.09	1.16±0.15	1.16±0.74	1.14±0.29

* All values are expressed as mean± standard deviation, n=5

Table 4. Evaluation of Ramipril Granules (F1 to F6)

Parameters	C1	C2	C3	D1	D2	D3
Bulk density(gm/cm³)*	0.41±0.11	0.44±0.10	043±0.50	0.47±0.76	0.43±0.16	0.44±0.56
Tapped ensity(gm/cm³)	0.40±0.91	0.42±0.21	0.41±0.11	0.46±0.32	0.43±0.22	0.44±0.52
Bulkiness(gm/cm³)*	2.43±0.16	2.27±0.71	2.32±0.11	2.12±0.95	2.37±0.18	2.18±0.46
Angle of repose*	22.23±0.94	23.11±0.82	21.9±0.25	24.7±0.12	21.7±0.17	20.7±0.10
Compressibility index*	11.50±0.26	12.24±0.22	12.65±0.91	11.21±0.51	11.61±0.45	12.21±0.11
Hausener's index*	1.025	1.047	1.048	0.978	1.002	1.011

* All values are expressed as mean± standard deviation, n=5

Table 5. Evaluation of Nizatidine tablets (F1 to F6)

Parameters	A1	A2	A3	B1	B2	B3
Hardness*(kg/cm²)	5.01±0.14	5.04±0.29	5.12±0.09	5.09±0.61	5.04±0.31	5.09±0.23
Friability*(%)	0.36±0.04	0.24±0.06	0.21±0.04	0.23±0.05	0.29±0.03	0.25±0.05
Weight variation*(mg)	99.6±4.2	99.1±3.6	99.7±2.9	99.5±3.0	99.3±3.6	99.5±3.0
Content uniformity*(%)	99.45±0.33	97.12±0.12	99.23±0.27	99.48±0.11	96.13±0.23	99.18±0.11
Thickness* (mm)	3.1±0.03	3.3±0.29	3.2±0.51	3.4±0.31	3.2±0.26	3.2±0.51
Diameter*(mm)	7.12±0.02	7.21±0.03	7.34±0.02	7.19±0.05	7.28±0.01	7.36±0.01

*All values are expressed as mean ± standard deviation, n =5

RESULTS AND DISCUSSION

Evaluation of Nizatidine granules and tablets

The prepared granules for compression of matrix tablets were evaluated for their flow properties. The bulk density ranged between0.41 to 0.47gm/cm3.

Compressibility index (Korsmeyer, 1983) was found to be the range of 12.26 to 13.36. Angle of repose was within the range of 28.05 to 29.06and Hausners ratio ranged from 1.14 to 1.17. These above values indicate that the prepared granules were exhibited good flow properties. (Table no-3 &5)

Evaluation of Nizatidine granules and tablets: The prepared granules for compression of matrix tablets were evaluated for

their flow properties. The bulk density ranged between0.41 to 0.47gm/cm3. Tapped density was within the range of 0.40 to 0.46 gm/cm^3. Bulkiness was found to be the range of 2.12 to 2.43 gm/cm^3. Compressibility index was found to be the range of 11.21 to 12.65. Angle of repose was within the range of 20.07 to 24.07and Hausners ratio ranged from 0.978 to 1.048. These above values indicate that the prepared granules were exhibited good flow properties. (Table no-4 &6)

formulation PA1 was more thanPA2,PA3. The cumulative percentage of drug release in the formulation PA3 showed controlled release than PA1, PA2. A major role played in drug release was the polymer concentration. At higher polymer concentration, the drug release was prolonged than the lower concentration of the polymer. The graphical presentation data of the Ramipril matrix tablet formulations with polymer is shown in (Figure – I)

**Table 6. Evaluation of Ramipril tablets (F1 to F6)**

Parameters	C1	C2	C3	D1	D2	D3
Hardness*(kg/cm²)	5.11±0.14	5.06±0.29	5.07±0.09	5.02±0.61	5.04±0.31	5.20±0.23
Friability*(%)	0.46±0.04	0.34±0.02	0.11±0.01	0.22±0.05	0.27±0.03	0.23±0.05
Weight variation*(mg)	98.6±4.2	99.1±3.6	99.2±2.9	99.0±3.0	99.3±3.6	99.7±3.0
Content uniformity*(%)	98.45±0.33	98.12±0.12	98.23±0.27	99.28±0.11	96.73±0.23	98.18±0.11
Thickness* (mm)	3.4±0.03	3.1±0.29	3.3±0.51	3.2±0.31	3.3±0.26	3.2±0.51
Diameter*(mm)	7.10±0.02	7.41±0.03	7.14±0.02	7.39±0.05	7.18±0.01	7.26±0.01

*All values are expressed as mean ± standard deviation, n =5

Table 7. Cumulative percentage of drug release from Nizatidine matrix tablet in combination of two different polymers in two different dissolution methods

Time(hrs)	Cumulative percentage drug release *											
	Nizatidine :HPMCK4M						Nizatidine : Guargum					
	Paddle method			Basket method			Paddle method			Basket method		
	PA1	PA2	PA3	BA1	BA2	BA3	PB1	PB2	PB3	BB1	BB2	BB3
1	17.6	15.1	13.9	17.9	15.8	13.5	14.4	13.2	12.2	14.9	13.9	13.2
2	23.1	22.0	21.2	23.7	21.7	20.6	22.2	21.8	20.6	23.1	22.0	21.6
3	31.7	29.6	28.1	32.4	28.4	27.3	29.0	27.8	24.8	29.8	28.2	26.9
4	39.2	37.3	36.0	40.2	37.2	36.7	37.1	36.6	35.6	38.0	36.3	35.7
5	44.6	43.7	41.9	45.6	43.1	41.5	42.2	41.8	40.6	43.3	43.4	42.6
6	50.9	48.9	45.6	49.5	51.0	45.0	46.6	44.0	43.8	47.2	45.6	45.0
7	58.1	56.4	55.3	57.8	58.9	54.8	56.8	54.9	53.1	57.1	54.1	53.8
8	64.6	63.6	61.2	65.2	63.1	61.8	62.2	61.2	60.5	63.0	60.8	59.1
9	70.9	69.3	68.0	70.4	68.7	69.6	69.4	68.0	67.0	70.4	69.0	68.4
10	78.6	76.1	75.3	77.7	75.2	76.7	75.9	75.3	74.2	74.8	73.4	73.0
11	86.9	85.6	83.1	87.6	84.5	84.7	84.4	83.2	82.2	84.0	83.4	82.0
12	92.4	90.2	87.1	91.9	89.6	88.8	88.7	86.7	84.8	89.8	87.31	86.0

Note- (i) Nizatidine: HPMCK4M   PA1, PA2, PA3- Formulation-1, 2,3 (Paddle method)
BA1, BA2, BA3- Formulation-1, 2, 3 (Basket method)
Nizatidine: Guargum   PB1, PB2, PB3 - Formulation-1, 2,3 (Paddle method)
BB1, BB2, BB3 - Formulation-1, 2, 3 (Basket method)
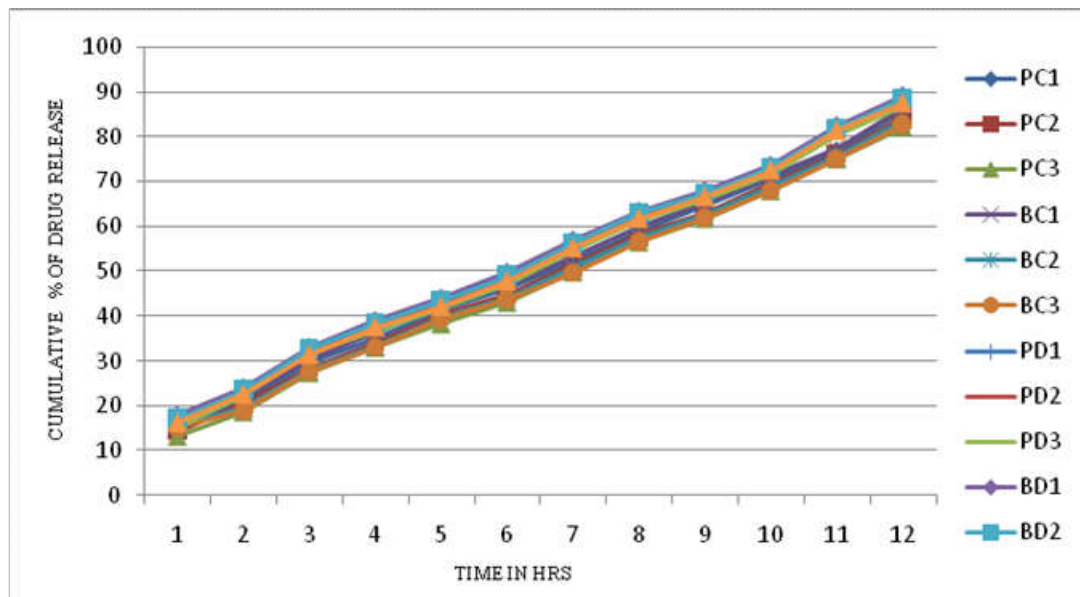
Figure 1. Percentage drug release of Nizatidine matrix tablet formulations

Case-1 : The percentage drug release of all formulations after 12 hours using HPMC K4M as polymer and paddle method was found to be 85.9% (PA1),84.4% (PA2), 87.1 (PA3) It was found that the cumulative percentage drug release[1] in the

1. **Case-(ii):** The percentage drug release of all formulations after 12 hours using HPMC K4M as polymer and Basket method was found to be 91.9% (BA1), 89.6% (BA2), 88.8% (BA3) It was found that the cumulative percentage drug release in the

formulation BA1 was more thanBA2,BA3. The cumulative percentage of drug release in the formulation BA3 showed controlled release than BA1, BA2.

2. **Case (III):** The percentage drug release of all formulations after 12 hours using Guargum as polymer and paddle method was found to be 88.74% (PB1), 86.7% (PB2), 84.8 (PB3) It was found that the cumulative percentage drug release in the formulation PB1 was more thanPB2,PB3. The cumulative percentage of drug release in the formulation PB3 showed controlled release than PB1, PB2.

3. **Case-(IV) :** The percentage drug release of all formulations after 12 hours using Guargum as polymer and Basket method was found to be 89.8% (BB1), 87.3% (BB2), 86.0 (BB3) It was found that the cumulative percentage drug release in the formulation BB1 was more thanBB2,BB3. The cumulative percentage of drug release in the formulation BB3 showed controlled release thanBB1, BB2.

4. Above all cases I, ii, iii, iv. A major role played in drug release was the polymer concentration [20]. At higher polymer concentration, the drug release was prolonged than the lower concentration of the polymer. In dissolution methods [18] like paddle method was controlled release compare to basket method, but very slight difference was arising.
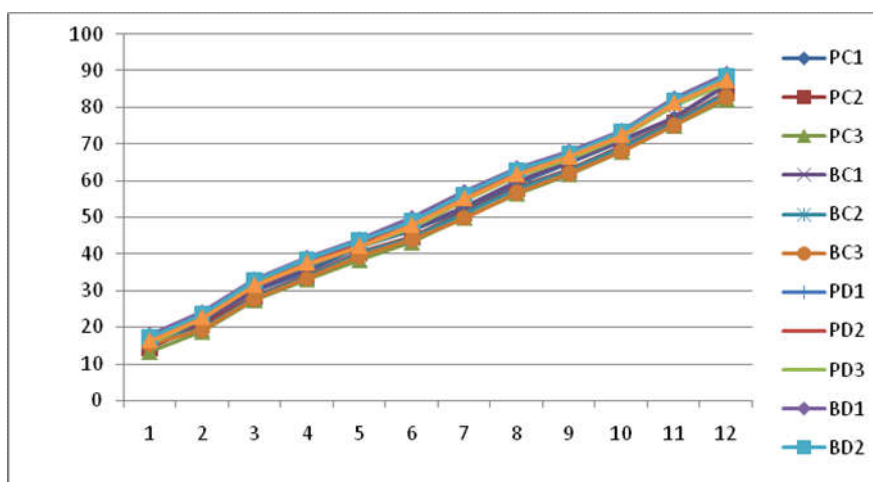
Case-1 : The percentage drug release of all formulations after 12 hours using HPMC K15M as polymer and paddle method was found to be 85.9% (PC1), 84.4% (PC2), 82.1 (PC3) It was found that the cumulative percentage drug release in the formulation PC1 was more thanPC2,PC3. The cumulative percentage of drug release in the formulation PC3 showed controlled release than PC1, PC2

1. **Case-(ii):** The percentage drug release of all formulations after 12 hours using HPMC K15M as polymer and Basket method was found to be 86.4% (BC1), 83.9% (BC2), 82.9% (BC3) It was found that the cumulative percentage drug release in the formulation BC1 was more thanBC2,BC3. The cumulative percentage of drug release in the formulation BC3 showed controlled release than BC1, BC2.

2. **Case -(III):** The percentage drug release of all formulations after 12 hours using Guargum as polymer and paddle method was found to be 88.2% (PD1), 87.6% (PD2), 86.7% (PD3) It was found that the cumulative percentage drug release in the formulation PD1 was more thanPD2,PD3. The cumulative percentage of drug release in the formulation PB3 showed controlled release than PB1, PB2.

Table 8. Cumulative percentage of drug release from Ramipril matrix tablet in combination of two different polymers in two different dissolution methods

Time(hrs)	Cumulative percentage drug release *											
	Ramipril :HPMCK15M						Ramipril : karayagum					
	Paddle method			Basket method			Paddle method			Basket method		
	PC1	PC2	PC3	BC1	BC2	BC3	PD1	PD2	PD3	BD1	BD2	BD3
1	15.6	14.4	13.1	16.2	15.7	15.2	17.4	16.9	15.4	17.9	17.1	16.2
2	21.1	20.6	18.6	21.8	19.7	19.0	23.7	23.0	22.4	24.1	23.6	22.5
3	29.7	28.6	27.3	30.3	28.0	27.6	32.7	32.1	31.7	33.1	32.7	31.4
4	35.2	34.3	33.0	36.2	33.6	33.1	38.2	37.4	36.9	39.0	38.5	37.5
5	41.6	40.5	38.2	42.5	40.0	39.4	43.7	42.9	42.0	44.0	43.6	42.1
6	46.2	44.9	43.0	46.8	44.2	43.9	49.0	48.1	47.3	49.8	49.0	47.8
7	52.1	51.6	49.8	53.0	50.9	49.7	56.2	55.5	54.6	56.9	6.2	55.1
8	59.0	58.2	56.4	59.8	57.6	56.7	62.9	62.1	61.4	63.4	62.9	61.7
9	64.7	63.1	61.7	65.2	62.7	62.0	67.2	66.7	66.0	67.9	67.3	66.5
10	70.6	69.7	67.8	71.4	68.9	68.0	73.0	72.6	71.8	73.6	73.2	72.4
11	76.9	76.1	75.0	77.4	75.8	751	81.7	81.0	80.3	82.4	81.8	81.2
12	85.9	84.4	82.1	86.4	83.8	82.9	88.2	87.6	86.8.	89.1	88.5	87.4

Note- (i) Ramipril: HPMCK15M   PC1, PC2, PC3- Formulation-1, 2, 3 (Paddle method)
                                   BC1, BC2, BC3- Formulation-1, 2, 3 (Basket method)
     Ramipril: Karayagum PD1, PD2, PD3 - Formulation-1, 2, 3 (Paddle method)
                          BD1, BD2, BD3 - Formulation-1, 2, 3 (Basket method)

Figure 2. Percentage drug release of Ramipril matrix tablet formulations

Table 9. Mechanical calibration parameters: Dissolution rotating paddle method

S.no	Calibration parameters	PDG harmonized Pharmacopoeial specification (USP,BP,JP)	FDA recommendations based on ASTM standard
1	Shaft wobble[9]	Rotation smoothly without significant wobble	≤1 .0 mm total run out
2	Shaft vertically	N/A	Bubble must be within the lines of bubble level (≤0.5 from vertical)
3	Vessel/ Shaft centering	≤ 2.0 mm from centre line	≤ 1.0 mm from centre line measured at an upper and lower possible
4	Vessel vertically	N/A	≤ 1.0 from vertical
5	Height/Paddle depth	25℃ ± 2 mm	25℃ ± 2 mm
6	Rotational speed	± 4 % from target	± 2 rpm from target

Table 10. Mechanical calibration parameters: Dissolution Basket method

S.no	Calibration parameters	PDG harmonized Pharmacopoeial specification (USP,BP,JP)	FDA recommendations based on ASTM standard
1	Shaft wobble	Rotation smoothly without significant wobble	≤1 .0 mm total run out
2	Shaft vertically	N/A	Bubble must be within the lines of bubble level (≤0.5 from vertical)
3	Vessel/ Shaft centering	≤ 2.0 mm from centre line	≤ 1.0 mm from centre line measured at an upper and lower possible
4	Vessel vertically	N/A	≤ 1.0 from vertical
5	Height/Paddle depth	25℃ ± 2 mm	25℃ ± 2 mm
6	Rotational speed	± 4 % from target	± 2 rpm from target
7	Basket wobble	± 1.0 mm run out	≤ 1.0 mm total runout

3. **Case-(IV) :** The percentage drug release of all formulations after 12 hours using Guargum as polymer and Basket method was found to be 89.1% (BD1), 88.5% (BD2), 87.4% (BD3) It was found that the cumulative percentage drug release in the formulation BD1 was more than BD2,BD3. The cumulative percentage of drug release in the formulation BD3 showed controlled release than BD1, BD2.

4. Above all cases I, ii, iii, IV. A major role played in drug release was the polymer concentration. At higher polymer concentration, the drug release was prolonged than the lower concentration of the polymer. In dissolution methods like paddle method was controlled release compare to basket method, but very slight difference was arising in both methods.

Conclusion

The results of experimental studies of Nizatidine and Ramipril matrix tablets proved that the granules are showed good flow properties, evaluation tests of tablets are within the acceptable limits, Infra Red (IR) spectral analysis [5] proved that there was no polymer- drug interaction, all the formulations of kinetic studies were followed zero order drug release and stability analysis revealed that all formulations were found to be stable after storing at 45° ± 2°C, 75±5% RH up to 45 days. A major role played in drug release was the polymer concentration. At higher polymer concentration, the drug release was prolonged than the lower concentration of the polymer. In dissolution methods like paddle method was controlled release compare to basket method, but very slight difference was arising in both methods

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