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A Study on Granules for Oral Suspension of Fixed Dose Combination of Analgesic Activities

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Keywords: Paracetamol, Mefenamic acid, Granules, wet granulation, analgesics etc.

Abstract:

Paracetamol and Mefenamic acid Granules for Oral Suspension formulation was prepared by granulation method. These two drugs are used as analgesics and the combination of the drug will increase the pharmacological activity. The formulations were prepared based on the release of the drug and taste of the suspension. These granules have shown increased bioavailability. The solubility of the drug can be increased. The granules formed by wet granulation using rapid mixer granulator have greater drug release. This type of formulation is not available in market. The drugs Paracetamol and Mefenamic acid are compatible with each other. The dosage form is Granules for Oral Suspension, so it should be dispensed in sachet, a readily available dosage form, which does not Effect the stability of drug. It is a unit dosage form, so it avoids over dosing. The drug release was rapid and has good pharmacological action.

Introduction

The Granules and powders are themselves in dosage forms. Powders and granules can be filled into sachets and be administered as a dosage form. They can also bean intermediary for drugs normally administered as a solution or suspension in an aqueous vehicle. They are also the intermediate products in the manufacture of other dosage forms. Most pharmaceutical granules have a short lifetime before being incorporated into tablets or hard-gelatin capsule dosage forms. Granules are agglomerates of powdered materials prepared into larger, free flowing particles. The shape of granules is generally irregular,[1,2]

Formulation of Granules:

Granulation is the process in which dry primary powder particles (i.e. single, discrete powder particles) are processed to adhere to form larger multi-particle entities called granules. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on the subsequent use of the granules. In the

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majority of cases, when granules will be made as an intermediate product, they have a size range towards the lower end of this spectrum typical between 0.2 and 0.5 mm^3.

Materials And Methods:

Evaluation of Paracetamol and Mefenammic AcidGranules for Oral Suspension:

- Evaluation of Paracetamol and Mefenammic AcidGranules for Oral Suspension includes

1. Production Yield
2. Dispersion
3. Taste
4. Dissolution by HPLC
5. Assay by HPLC

6.11 Particle size analysis

6.12 Production Yield:

Production yield of every batch was calculated by usingtheoretical and practical yield.

Percentage yield = practical yield / theoretical yield *100

6.13 Taste:

Taste of suspension was observed physically. The granules present in the sachet were poured in 200 mL of water.

6.14 Dispersion:

Dispersion of suspension was observed physically. The granules present in the sachet were poured in 200 mL of water.

6.15 Dissolution by HPLC:

Dissolution Parameters:

Dissolution medium : pH 9.0 tris buffer + 1.0 %
SLSVolume : 900 mL
Apparatus : USP II (paddle)
Temperature : 37±5°C
RPM : 50 rpm
Time points : 5, 10, 15, 30, 45 and 60 minSample with drawn : 10 mL
Dissolution Medium replaced: 10 mL

Chromatographic conditions:

Column : Inertsil ODS-3V (150 x 4.6 mm, 5µm)Flow rate : 1.0 mL/mL
Injection volume : 10 µl
Wavelength : 270 nm
Column temperature : 305°C
Elution Mode :
Gradient
Run time : 15 min

Procedure:

- Equilibrate the dissolution medium to 37 ± 0.5°C.
- Accurately weigh and transferred target weight in to dissolution medium.
- At each time stated, withdraw a sample volume specified in dissolution parameters .
- Replace the aliquots withdrawn for analysis with equal volumes of fresh dissolution medium at 37 ± 0.5°C.
- Keep the vessel covered for the duration of the test and verify the temperature of the mixture under test at suitable times.
- Filter the collected samples through 0.45 µm Nylon syringe filter and inject to HPLC.

6.16 Assay by HPLC:

Chromatographic conditions:

Column : Water X-Bridge Shield RP(150 x 4.6 mm, 5µm).
Flow rate : 1.0 mL/mL.
Injection volume : 10 µl.
Wavelength : 270 nm.
Column temperature : 30±5°C.
Elution Mode : Gradient.
Run time : 15 min.

Preparation of Blank:

Transfer 10 mL pH 1.0 buffer in to 100 mL volumetricflask and makeup volume with diluent

Preparation of standard solution:

Accurately weight and transfer 25 mg of Mefenamic acid and 50 mg of Paracetamol working standard or reference standard into 100 mL volumetric flask. Add 10 mL pH 1.0 buffer sonicate for about 5 min and then add 60 mL of diluent and sonicate about 5 min makeup the volume with diluent.

Test Preparation:

Test not less than 10 sachets and mix properly in butter paper. Weigh and transfer equivalent to 500 mg of paracetamol into 1000mL volumetric flask, add 100mL pH 11.0 buffer swirl manually for 2 min then sonicate for about 10 min add 600 mL of diluent and sonicate for about 30 min with intermediate shaking.

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Sample Injection:

Equilibrate the HPLC system with mobile phase and inject the sample.

6.17 Particle size analysis:

- Weigh100 gm of finished blends and places it in thesieves.
- The sieves used were ASTM # 20, 30, 40, 60, 80,100, 120 and 200 meshes.
- Place the sieves in ascending order of sieve no.
- The parameters used were

1. Time: 10 min.
2. Amplitude : 10
3. Weight : 100 gm

- Cumulative % was calculated.

Results

- **7.1 Production Yield:**
- Production yield of all batches were calculated byusing theoretical and practical yield

Batch No.	Percentage yield
PM-1	98.93
PM-2	93.98
PM-3	96.5
PM-4	94.7
PM-5	94.67
PM-6	96.67
PM-7	98.03
PM-8	97.98
PM-9	98.34

Table 1: Table of production yield

- **7.2 Dispersion:**
- Dispersion of suspension was physically observed.

Table 2: Table of results of dispersion

Batch No.	Dispersion
PM-1	Contents not easily dispersed
PM-2	Contents were easily dispersed
PM-3	Contents were easily dispersed
PM-4	Contents were easily dispersed
PM-5	Contents were easily dispersed
PM-6	Contents were easily dispersed
PM-7	Contents were easily dispersed
PM-8	Contents were easily dispersed
PM-9	Contents were easily dispersed

- **7.3 Taste:**
- Taste of the suspension was observed physically.

	PM-1	PM-2	PM-3	PM-4	PM-5	PM-6	PM-7	PM-8	PM-9
v-1	2	2	2	2	2	3	4	5	5
v-2	2	2	2	3	3	3	3	5	5
v-3	2	2	3	2	2	2	4	5	5
v-4	2	2	2	2	3	3	4	4	5
v-5	2	2	2	3	2	3	3	5	5
v-6	2	2	2	2	3	3	4	5	5
Average	2	2	2.1	2.3	2.5	2.8	3.6	4.8	5

Table 3: Table for evaluation of taste

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➢ **Note: 5- Excellent, 4- Good, 3- Satisfactory, 2- Bitter, 1- No taste.**

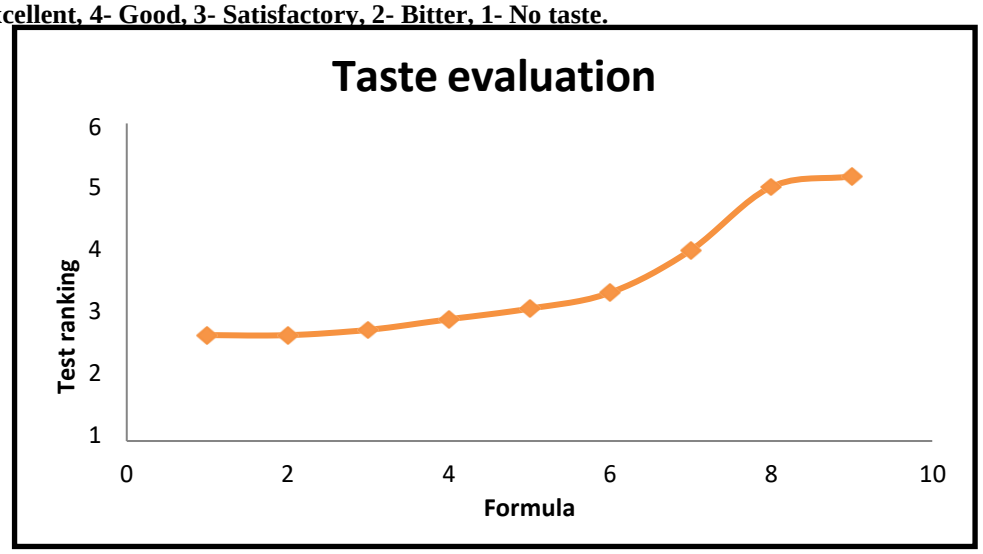

Fig. 1: Taste evaluation graph

Dissolution results:

Dissolution studies were conducted to get the percentage drug release in particular formula in a particular medium.

Dissolution of Panadol Tablets:

Panadol Tablets			
S. No.	**Time points**	**Mean**	**% RSD**
1	5	70	4.8
2	10	76	3.1
3	15	82	2.6
4	30	92	2.5
5	45	96	1.9
6	60	99	1.6
7	90	100	1.2
8	Inf	100	0.9

Table 4: Dissolution of Panadol Tablets

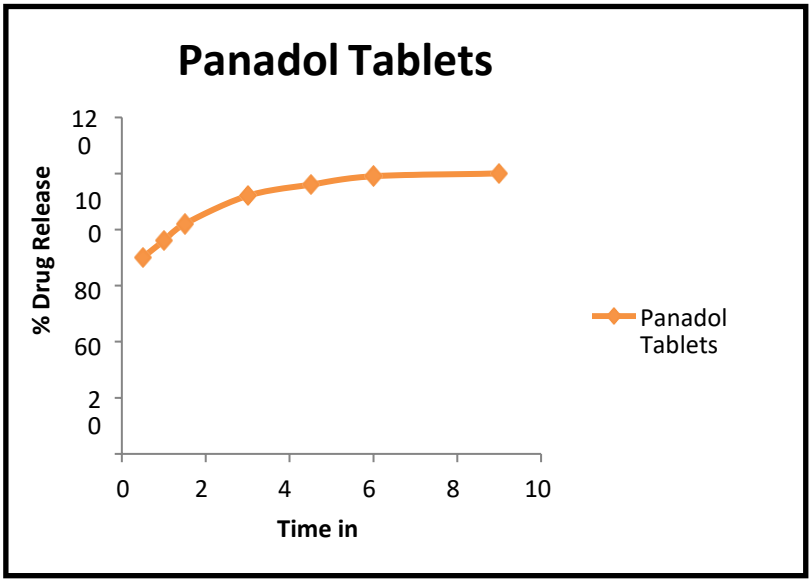

Fig. 2: Dissolution Graph of Panadol Tablets

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Dissolution of Mefenmic acid Suspension:

Mefenamic acid Suspension			
S. No.	**Time points**	**Mean**	**% RSD**
1	5	72	2.4
2	10	78	1.9
3	15	80	3.8
4	30	85	2.7
5	45	95	3
6	60	98	2.5
7	90	99	1
8	Inf	100	0.8

Table 5: Dissolution of Mefenamic acid Suspension

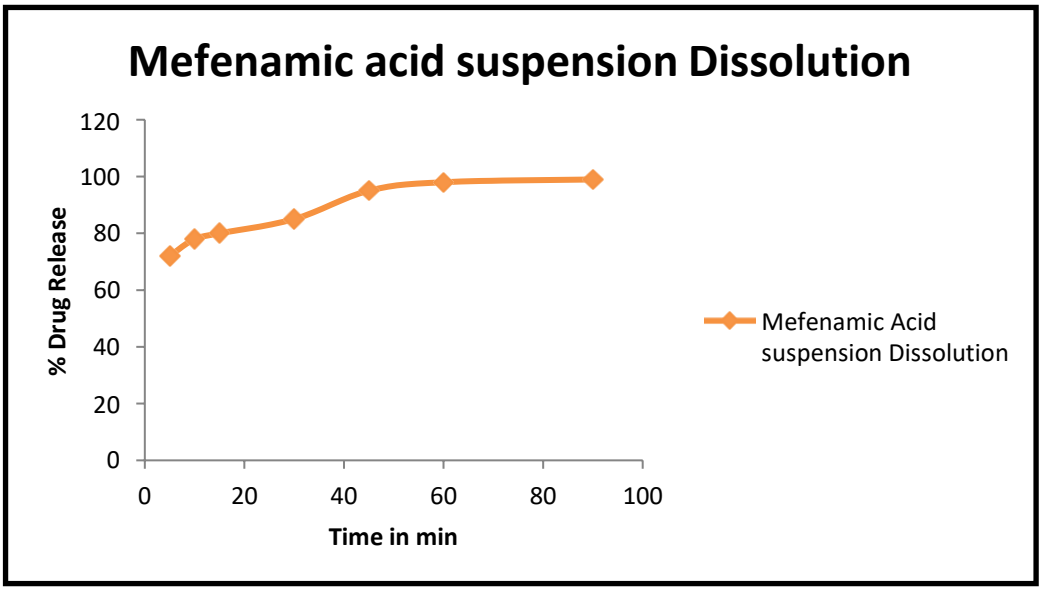

Fig. 3: Dissolution Graph of Mefenamic acid suspension

PM-1: Dissolution of Paracetamol and Mefenamic acid by using pH 9.0 tris buffer + 1.0 % SLS and USP II (paddle) at 37±5ºC.

Batch No- PM 1		Paracetamol		Mefenamic Acid	
S. No.	**Time points**	**Mean**	**% RSD**	**Mean**	**% RSD**
1	5	83	3.4	79	3
2	10	90	2.8	80	2.8
3	15	93	1.6	82	1.9
4	30	95	0.8	85	0.3
5	45	95	0.7	89	0.7
6	60	96	0.8	90	0.3
7	90	99	0.7	97	0.9
8	Inf	99	0.6	97	0.3

Table 6: Dissolution of Paracetamol and Mefenamic acid of PM-1

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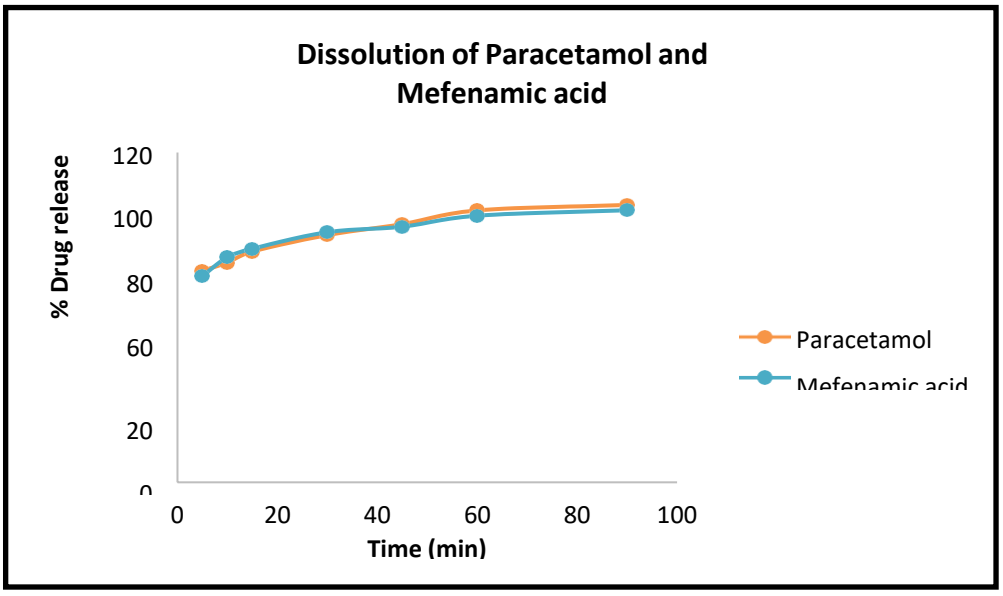

Fig. 4: Dissolution graph of PM-1

PM-2: Dissolution of Paracetamol and Mefenamic acid by using pH 9.0 tris buffer + 1.0 % SLS and USP II (paddle) at 37±5ºC.

Batch No- PM 2		Paracetamol		Mefenamic acid	
S. No.	Time points	Mean	% RSD	Mean	% RSD
1	5	65	2.5	59	2.4
2	10	69	2.8	62	3.1
3	15	73	1.6	69	1.9
4	30	85	0.9	73	0.1
5	45	89	1	78	0.5
6	60	90	1.2	85	0.3
7	90	93	0.7	90	1
8	Inf	95	0.6	90	0.5

Table 7: Dissolution of Paracetamol and Mefenamic acid of PM-2

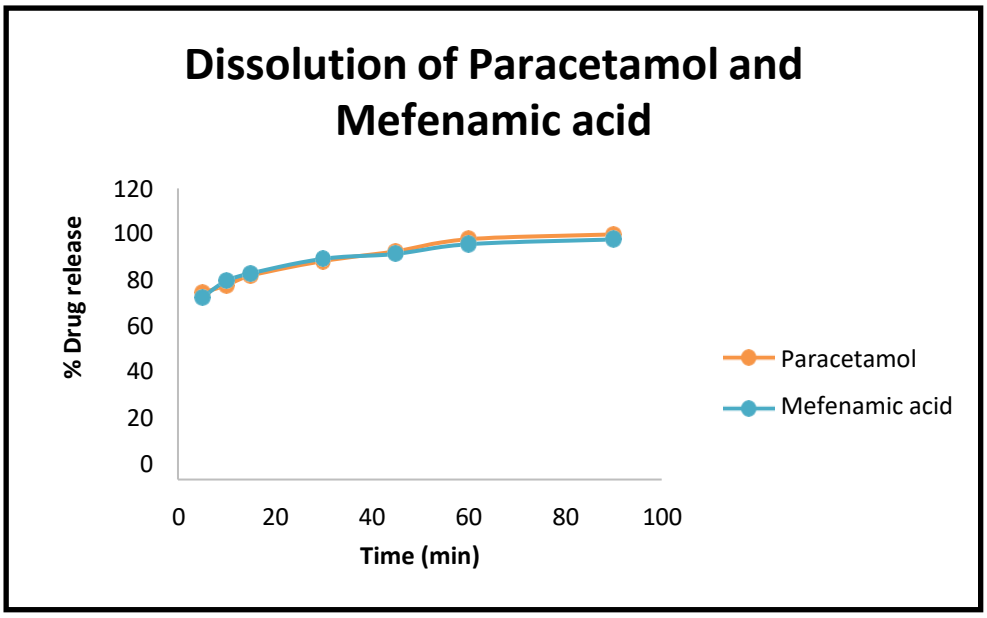

Fig. 5: Dissolution graph of PM-2

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PM 3: Dissolution of Paracetamol and Mefenamic acid by using pH 9.0 tris buffer + 1.0 % SLS and USP II (paddle) at 37±5ºC.

Batch No- PM 3		Paracetamol		Mefenamic acid	
S. No.	Time points	Mean	% RSD	Mean	% RSD
1	5	69	2.5	67	2.4
2	10	70	2.8	75	3.1
3	15	74	1.6	79	1.9
4	30	87	0.9	82	0.1
5	45	90	1	85	0.5
6	60	94	1.2	87	0.3
7	90	96	0.7	94	1
8	Inf	97	0.6	94	0.5

Table 8: Dissolution of Paracetamol and Mefenamic acid of PM-3

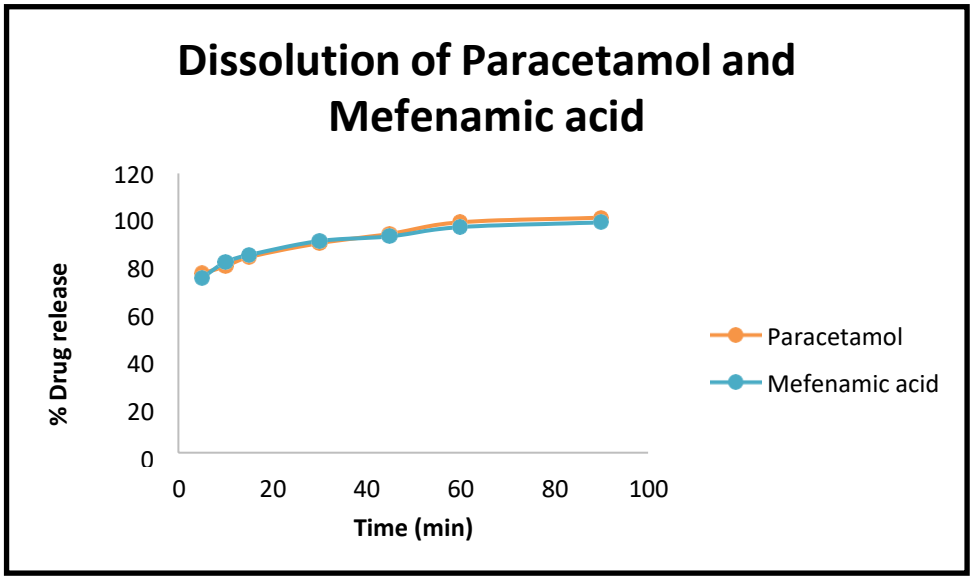

Fig. 6: Dissolution graph of PM-3

PM 4: Dissolution of Paracetamol and Mefenamic acid by using pH 9.0 tris buffer + 1.0 % SLS and USP II (paddle) at 37±5ºC.

Batch No- PM 4		Paracetamol		Mefenamic acid	
S. No.	Time points	Mean	% RSD	Mean	% RSD
1	5	71	4.1	67	6.8
2	10	76	3.1	74	3.6
3	15	80	2.4	79	1.9
4	30	84	1.8	82	0.7
5	45	89	1.2	87	0.6
6	60	92	2.1	90	0.2
7	90	96	0.7	93	1.7
8	Inf	96	0.9	96	0.5

Table 9: Dissolution of Paracetamol and Mefenamic acid of PM-4

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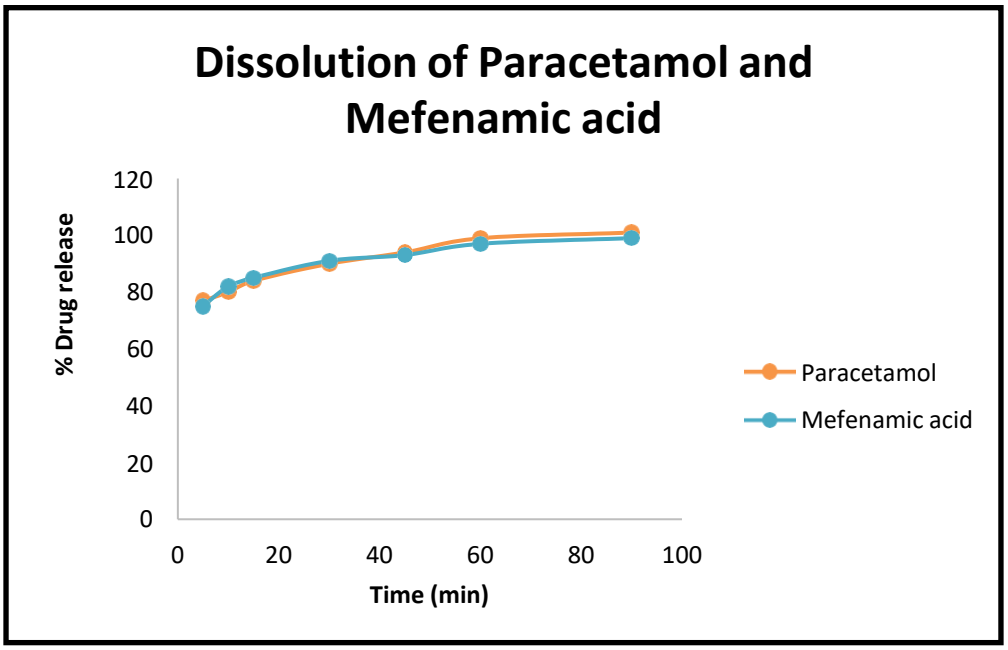

Fig. 7: Dissolution graph of PM-4

PM 5: Dissolution of Paracetamol and Mefenamic acid by using pH 9.0 tris buffer + 1.0 % SLS and USP II (paddle) at 37±5ºC.

Batch no- PM 4		Paracetamol		Mefenamic acid	
S. No.	Time points	Mean	% RSD	Mean	% RSD
1	5	64	1.8	57	6.8
2	10	69	2.8	62	2.9
3	15	74	2.4	71	0.6
4	30	79	0.8	75	1.3
5	45	81	4.1	79	1.5
6	60	85	2.1	80	2.3
7	90	86	0.7	80	0.3
8	Inf	89	4	84	3

Table 10: Dissolution of Paracetamol and Mefenamic acid of PM-5

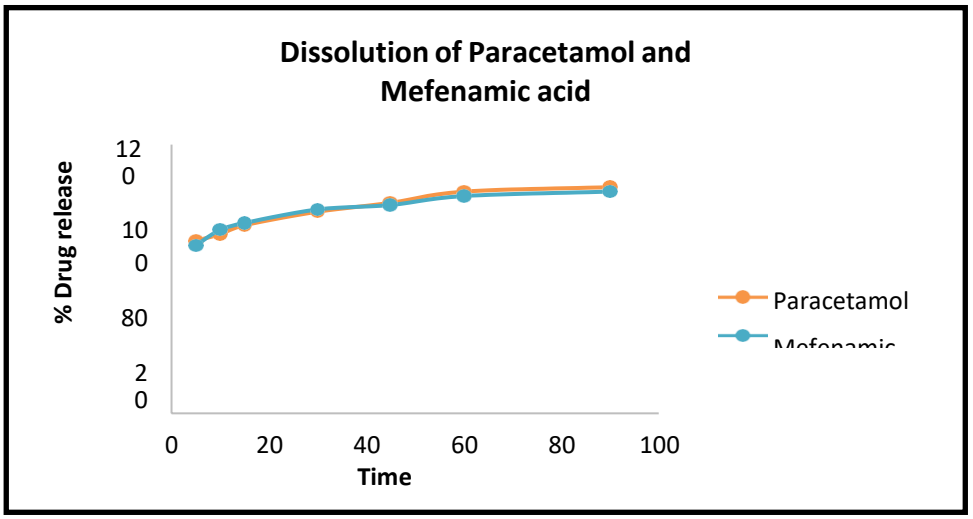

Fig. 8: Dissolution graph of PM-5

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PM 6: Dissolution of Paracetamol and Mefenamic acid by using pH 9.0 tris buffer + 1.0 % SLS and USP II (paddle) at 37±5ºC.

Batch no- PM 6		Paracetamol		Mefenamic acid	
S. No.	Time points	Mean	% RSD	Mean	% RSD
1	5	65	1.5	63	2.6
2	10	72	1.2	70	3.4
3	15	79	2.6	76	3.2
4	30	82	2.5	81	1.4
5	45	87	3.7	82	3.8
6	60	90	1.6	92	2.5
7	90	93	1.6	92	1.3
8	Inf	94	2.7	92	1.5

Table 11: Dissolution of Paracetamol and Mefenamic acid of PM-6

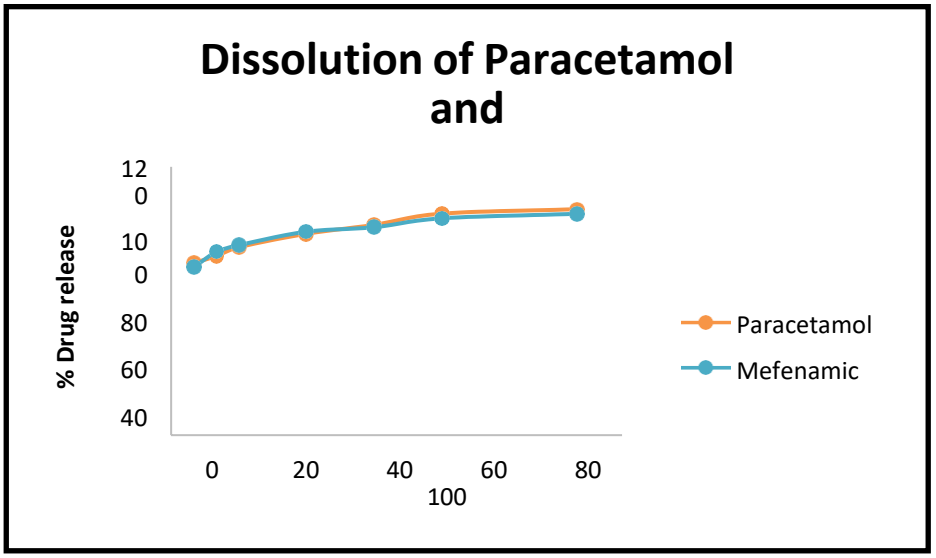

Fig. 9: Dissolution graph of PM-6

PM 7: Dissolution of Paracetamol and Mefenamic acid by using pH 9.0 tris buffer + 1.0 % SLS and USP II (paddle) at 37±5ºC.

Batch No- PM 7		Paracetamol		Mefenamic acid	
S. No.	Time points	Mean	% RSD	Mean	% RSD
1	5	73	1.5	63	2.6
2	10	78	1.2	70	3.4
3	15	81	2.6	76	3.2
4	30	86	2.5	81	1.4
5	45	90	3.7	84	3.8
6	60	93	1.6	90	2.5
7	90	95	1.6	92	1.3
8	Inf	96	2.7	93	1.5

Table 12: Dissolution of Paracetamol and Mefenamic acid of PM-7

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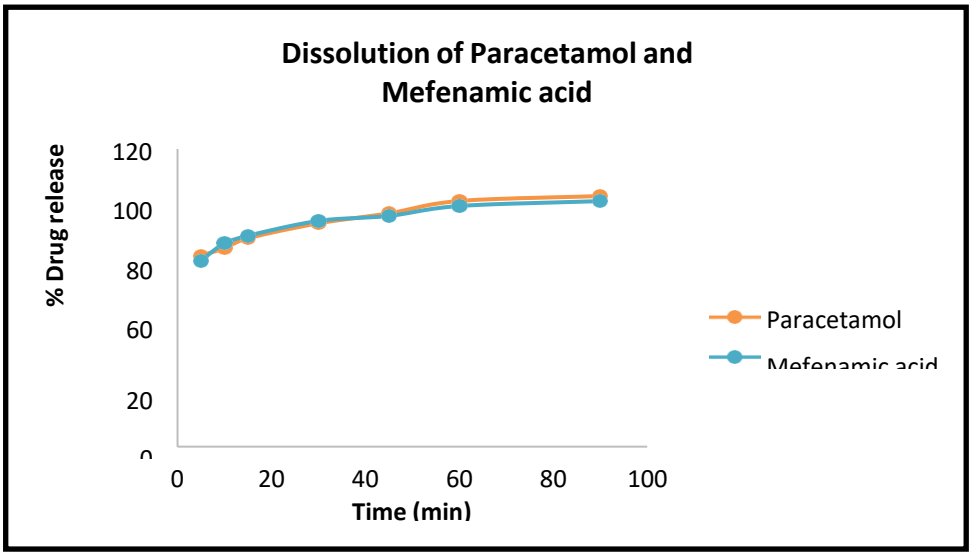

Fig. 10: Dissolution graph of PM-7

PM 8: Dissolution of Paracetamol and Mefenamic acid by using pH 9.0 tris buffer + 1.0 % SLS and USP II (paddle) at 37±5ºC.

Batch No- PM 8		Paracetamol		Mefenamic acid	
S. No.	Time points	Mean	% RSD	Mean	% RSD
1	5	79	4.9	75	2.8
2	10	82	2.8	80	1.9
3	15	85	3.1	85	2.4
4	30	90	2.4	90	2.7
5	45	93	1.8	92	2.9
6	60	99	2.2	98	2.4
7	90	102	2.1	100	2.5
8	Inf	104	2.7	101	2.5

Table 13: Dissolution of Paracetamol and Mefenamic acid of PM-8

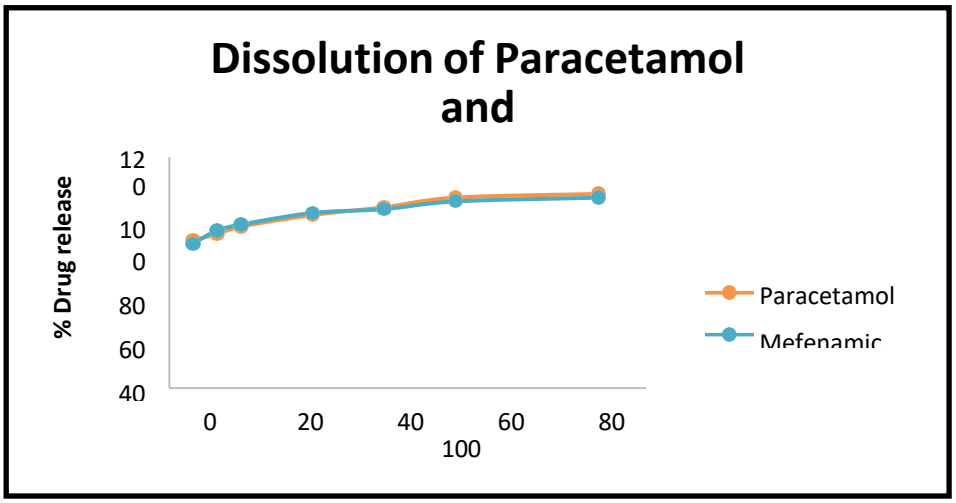

Fig. 11: Dissolution graph of PM-8

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PM 9: Dissolution of Paracetamol and Mefenamic acid by using pH 9.0 tris buffer + 1.0 % SLS and USP II (paddle) at 37±5ºC.

Batch No- PM 9		Paracetamol		Mefenamic acid	
S. No.	Time points	Mean	% RSD	Mean	% RSD
1	5	77	4.8	75	2.4
2	10	80	7.1	82	1.9
3	15	84	2.1	85	3.8
4	30	90	2.3	91	2.7
5	45	94	2.2	93	3
6	60	99	2.2	97	2.5
7	90	101	2.1	99	1
8	Inf	103	2.7	101	0.8

Table 14: Dissolution of Paracetamol and Mefenamic acid of PM-9

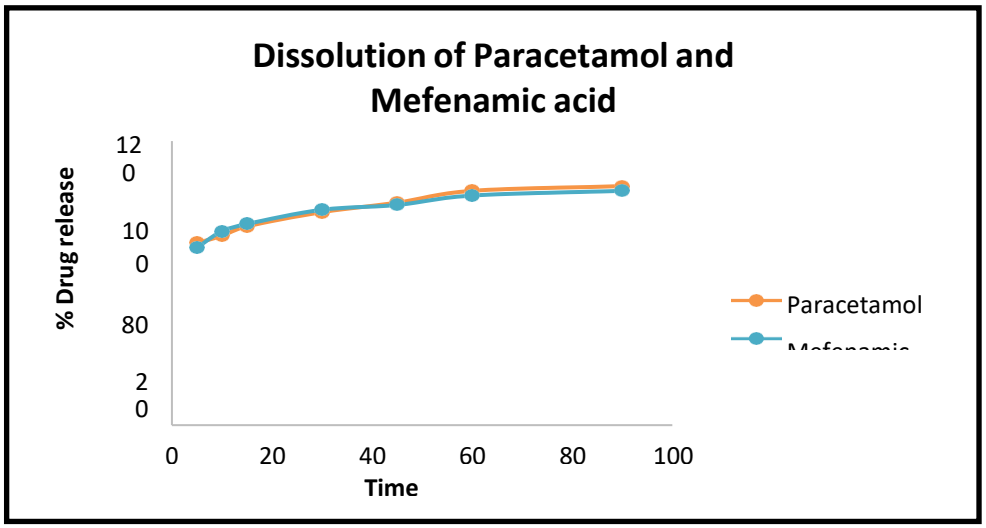

Fig. 12: Dissolution graph of PM-9

Comparison of Dissolution profile of Paracetamol and Mefenamic Acid with Innovator:

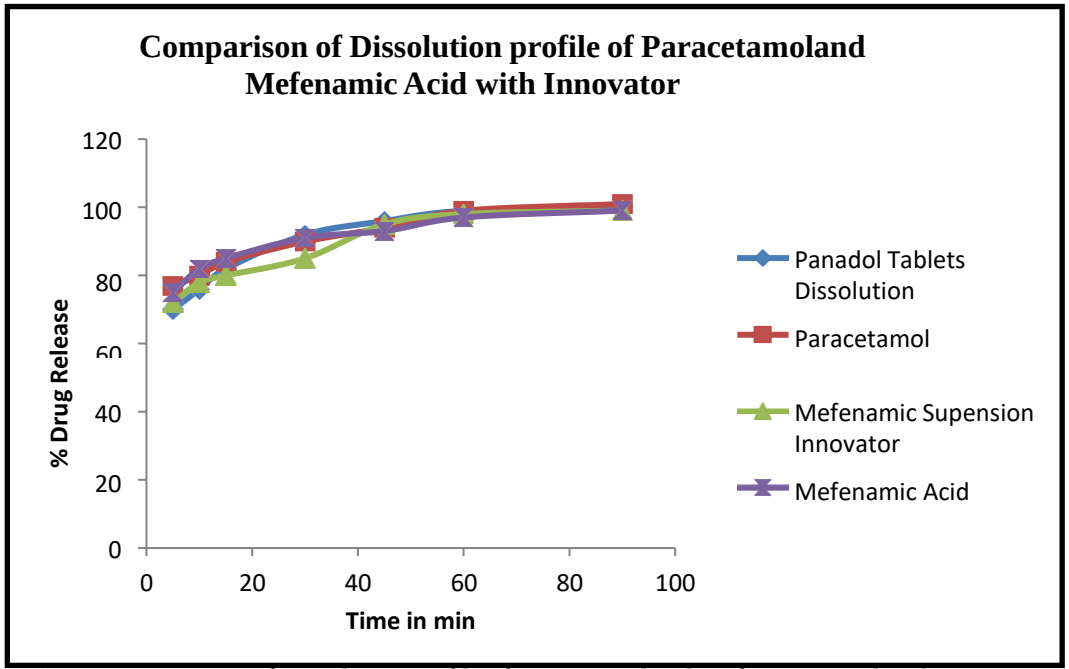

Fig. 13: Comparison of Dissolution profile of Paracetamol and Mefenamic Acid with Innovator

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- F_2 Value of Paracetamol was found to be 75.331.
- F_1 Value of Paracetamol was found to be 3.

F_2 Value of Mefenamic Acid was found to be 74.785.

- F_1 Value of Paracetamol was found to be 3.

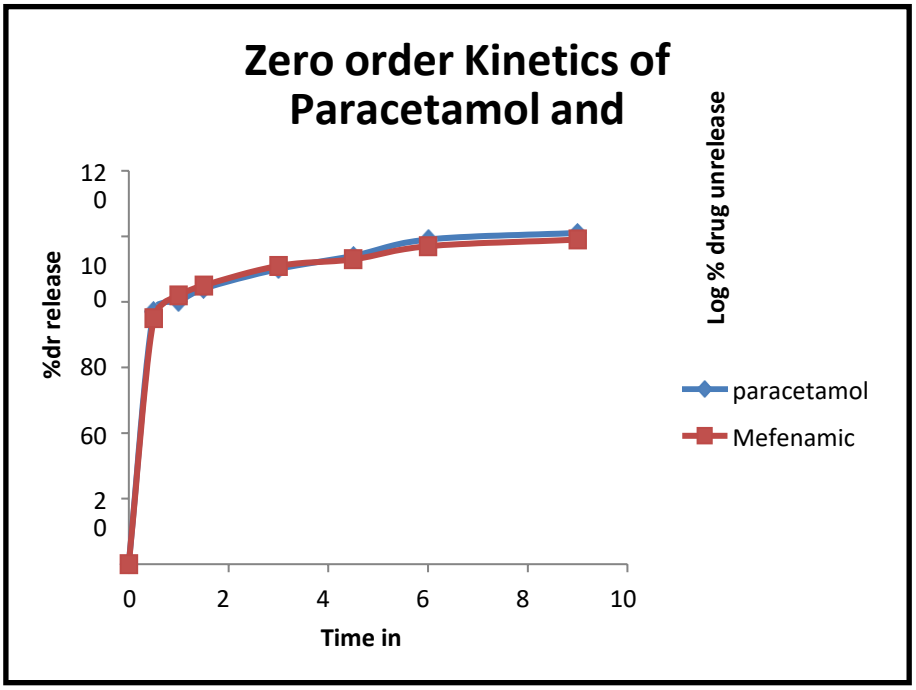

Fig. 14: Zero Order kinetics of Paracetamol and Mefenami

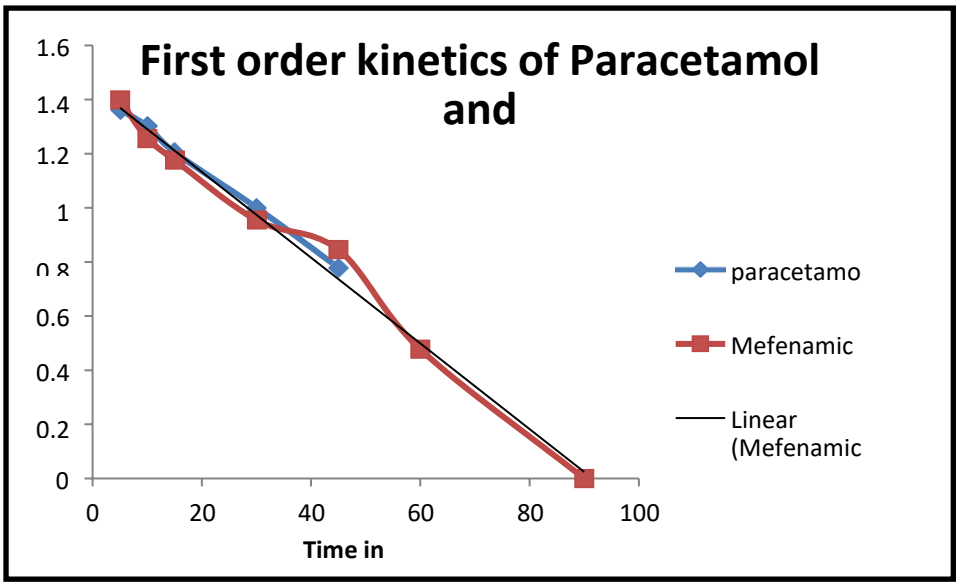

Fig. 15: First Order kinetics of Paracetamol and Mefenamic Acid

Discussion:

Paracetamol and Mefenamic acid granules were prepared by the granulation technique for better pharmacological action. The formulations were prepared based on the release of the drug & the taste of the suspension. The process involved in the preparation of different formulation, for PM-1 the method used wasDry mixing method, for PM-2 to PM-6 by fluid bed processor and for PM-7 to PM-9 by rapid mixer granulator.

Production Yield:

The results of production yield are in table. The percentage yield of PM-1 to PM-9 was in range

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of 93.98 to 98.93. The production yield was manageable with little loss of drug during the formulation stage.

PM-1:

For PM-1 the method used was dry mixing. Where only mixing of materials without any granule formation .the contents present in the sachet were not easily dispersed in water and it was bitter in taste. The assayof Paracetamol and Mefenamic acid were 99 and 97 respectively. The mean drug release was 95 and 85respectively after 30 min. The particle size lies between75 to 850 microns. But large part of granules size lies between 600 to 850 microns. Considering drug dispersion, taste and drug release the process is changed to fluid bed processor.

PM-2:

For PM-2 the method used was wet granulation by fluid bed processor. Here the binder solution sprayed on the material to get granules. The formed granules results white to off white color powder having bulk density 0.472 g/mL, tapped density 0.561 g/mL, carr's dispersion of the contents present in the sachet were easily dispersed in water and it was bitter in taste. The assay of Paracetamol and Mefenamic acid were 95 and

89 respectively. The mean drug release was 83 and 73respectively after 30 min. the particle size lies between 75 to 850 microns. But large part of granules size lies between 400 to 650 microns. As the taste was still bitter so the formula changed.

PM-3:

For PM-3 the method used was wet granulation by fluid bed processor. Here the binder solution sprayed on the material to get granules. The formed granules results white to off white color powder having bulk density 0.504 g/mL, tapped density 0.595 g/mL, carr's index 15.27% and hausner ratio 1.18. And the dispersion of the contents present in the sachet waseasily dispersed in water and it was bitter in taste. The assay of Paracetamol and Mefenamic acid were 96 and 90 respectively. The mean drug release was 87 and 82 respectively after 30 min. the particle size lies between 75 to 850 microns. But large part of granules size lies between 400 to 650 microns. As the taste was stillbitter so the formula changed.

PM-4:

For PM-4 the method used was wet granulation by fluid bed processor. Here the binder solution sprayed on the material to get granules. The formed granules results white to off white color powder having bulk density 0.504 g/mL, tapped density 0.595 g/mL, carr's index 15.27% and hausner ratio 1.18. And the dispersion of the contents present in the sachet waseasily dispersed in water and it was bitter in taste. The assay of Paracetamol and Mefenamic acid were 98 and 93 respectively. The mean drug release was 84 and 82 respectively after 30 min. the particle size lies between 75 to 850 microns. But large part of granules size lies between 400 to 650 microns. As the taste was stillbitter so the formula changed.

PM-5:

For PM-5 the method used was wet granulation by fluid bed processor. Here the binder solution sprayed on the material to get granules. The formed granules results white to off white color powder having bulk density 0.504 g/mL, tapped density 0.665 g/mL, carr's index 24.21% and hausner ratio 1.31. And the dispersion of the contents present in the sachet was easily dispersed in water and it was bitter in taste. The assay of Paracetamol and Mefenamic acid were 99 and 95 respectively. The mean drug release was 79 and 75 respectively after 30 min. the particle size lies between 75 to 850 microns. But large part of granules size lies between 400 to 650 microns. As the taste was still bitter so the formula changed.

PM-6:

For PM-6 the method used was wet granulation by fluid bed processor. Here the binder solution sprayed on the material to get granules. The formed granules results white to off white color powder having bulk density 0.574 g/mL, tapped density 0.665 g/mL, carr's index 16.21% and hausner ratio 1.27. And the dispersion of the contents present in the sachet was easily dispersed in water and taste was satisfied. The assay of Paracetamol and Mefenamic acid were 97 and 93 respectively. The mean drug release was 82 and 81 respectively after 30 min. the particle size lies between 75 to 850 microns. But large part of granules size lies between 400 to 650 microns. As the taste of the suspension was satisfied but the drug release was not satisfactory so the method of wet granulation was changed to rapid mixer granulator for the same formula.

PM-7:

For PM-7 the method used was wet granulation by rapid mixer granulator. The formed granules results

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light white to off white color powder having bulk density 0.606 g/mL, tapped density 0.833 g/mL, carr's index 27.27% and hausner ratio 1.375. And the dispersion of the contents present in the sachet was easily dispersed in water and taste was satisfied. The assay of Paracetamol and Mefenamic acid were 98 and 97 respectively. The mean drug release was 86 and 81 respectively after 30 min. the particle size lies between 75 to 850 microns. But large part of granules size lies between 400 to 650 microns. As the taste of the suspension was satisfied but the drug release was not satisfactory so the inter formula changes done.

PM-8:

For PM-8 the method used was wet granulation by rapid mixer granulator. The formed granules results light white to off white color powder having bulk density 0.635 g/mL, tapped density 0.845 g/mL, carr's index 27.345% and hausner ratio 1.255. And the dispersion of the contents present in the sachet was easily dispersed in water and taste was satisfied. The assay of Paracetamol and Mefenamic acid were 99.8 and 99 respectively. The mean drug release was 90 and 90 respectively after 30 min. the particle size lies between 75 to 850 microns. But large part of granules size lies between 400 to 650 microns. The drug release was satisfied.

PM-9:

For PM-9 the method used was wet granulation by rapid mixer granulator. The formed granules results light white to off white color powder having bulk density 0.620 g/mL, tapped density 0.750 g/mL, carr's index 18.46% and hausner ratio 1.23. And the dispersion of the contents present in the sachet was easily dispersed in water and taste was satisfied. The assay of Paracetamol and Mefenamic acid were 100.4 and 99.7 respectively. The mean drug release was 90 and 91 respectively after 30 min. the particle size lies between 75 to 850 microns. But large part of granules size lies between 400 to 650 microns. The drug release was satisfied. The F_2 value of Paracetamol was foundto be 75.787%. The F_1 value of Paracetamol was found to be 3%. The F_2 value of Mefenamic acid was found tobe 74.331%. The F_1 value of Mefenamic acid was found to be 3%.

Conclusion:

The granules for oral suspension were prepared by granulation method using povidone as binder and glucose moieties as taste masking actives. The formulations were prepared based on the release of the drug and major part is taste of suspension. As 9 formulations were prepared on modification to get a satisfied dosage PM-1 by dry mixing method, PM-2 to PM-6 by fluid bed processor by changing intragranular and extragranular excipients and its concentration, PM-7 to PM-9 by rapid mixer granulator by changing intragranular and extragranular excipients.

Particle size analysis is carried out by sieve analysis method. The granule was distributed in the size range of 75 to 850 microns. The major part of the granules lies in between 180 to 425 microns.

The granulated formulation dispersion was uniform & satisfactory. The granule size majorly affects the uniformity and dispersion of granules in water. When the granule size is larger then they easily dispersed in water. When the granules are fine then they float on the surface of water. The tastes of the suspension for PM-1 to PM-5 have bitter and for PM-6 to PM-9 have satisfied taste. The glucose moieties used in the formulation will mask the bitterness of the drugs.

The percentage yield of PM-1 to PM-9 was in range of 93.98 to 98.93. The production yield was manageable with little loss of drug during the formulation stage. Assay of Paracetamol and Mefenamic acid are the major consideration in the formulation development.Assay of both the drugs are 100 percent drug released when the formulation was prepared by wet granulationmethod using rapid mixer granulator. The assay ofParacetamol and Mefenamic acid were in range 95-100.5 and 90-99.7 respectively.

The dissolution of Granules for Oral Suspension was studied by using USP II apparatus. The mean drug release was high in case of formulation prepared by rapid mixer granulator.

PM-9 formulation was compared with innovator. As the Panadol tablets are innovator for paracetamol and Mefenamic acid suspension for Mefenamic acid and Nimesil GFOS for Paracetamol and Mefenamic acid GFOS. This formula having the flow properties resembling same as innovator flow properties. The F_2 value is also satisfactory as per the dissolution data of Paracetamol and Mefenamic acid with the innovators.

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