International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 5 Issue 3 ǁ June 2016 ǁ PP.07-12

Formulation and Evaluation of Fast Dissolving Tablets of Paracetamol Using Oats Powder

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ABSTRACT: *Paracetamol is a slightly water soluble drug belongs to BCS Class IV, used in various pain managements & in management of fever. The drug solubility was increased by solid dispersion method, in which two techniques namely physical mixing and co-grinding were tried at the ratios of 1:0.25, 1:0.5 & 1:0.75 for paracetamol to oats powder. Various parameters like pre & post compressional parameters were tested and final formula was selected based on disintegration time and in-vitro dissolution profile. Where, all the formulations were dispersed bellow 92 seconds and F_6 formulation was showing 100% release at 20th minute and faster compared to the marketed formulation. F_6 was prepared by co-grinding technique, at 1:0.75 paracetamol to oats powder ratio. F_6 is showing zero-order drug release and mechanism of release is Super case – II transport (n = 0.9738). All the formulations were prepared using direct compression method, a conventional method of preparation.*

Keywords: *Direct Compression, Fast Dissolving Tablets, Oats Powder, & Paracetamol.*

I. Introduction[1,2,3,4,5]

Tablets are oral solid dosage forms which are conveniently self administrable, and are stable among various dosage forms and pilfer proof in nature. Hence, an accurate dose can be administered effectively. Fast dissolving tablets are designed to increase the bioavailability of the poorly soluble drugs. These are conveniently administrable to the pediatric and geriatric patients who are suffering from swallowing of solid dosage forms orally. Paracetamol is a NSAID used in various pain managements alone or in-combination with other anti-inflammatory drugs. Paracetamol is slightly soluble in water and having low bioavailability, hence frequency of administration is high. Because of which the current study was designed to enhance the bioavailability of paracetamol using the mechanism of fast dissolution technique by co-grinding technique, an economical method and to decrease frequency of administration also. The fast dissolving tablets are prepared by direct compression method, a very economical method of preparation.

II. Materials & Methods

Materials: Paracetamol and all the chemicals were gifted by SK Health care Pvt. Ltd, Bolaram, Hyderabad. Oats was purchased from local sources.

Methods[6,7,8,9,10]

1. Analytical Method Development

1.1. Preparation of 0.1N HCl solution: 8.5 ml of conc. HCl was place in 1000 ml volumetric flask & volume make up to 1000 ml by using distilled water.

1.2. Determination of λ_{max} Paracetamol in 0.1N HCl solution: 100mg of Paracetamol was weighed and dissolved in 10ml 0.1N HCl and then make up to a volume of 100ml to get 1000µg/ml concentrated stock solution (working standard). From the working standard solution 10ml was diluted to 100ml with 0.1N HCl solution to get 100µg/ml concentrated solution (Dilution 1). From the dilution1, 1ml solution was diluted to 10ml with 0.1N HCl solution to get 10 µg/ml concentrated solution (Dilution 2). This solution was scanned at range of 200-400nm wavelength light corresponding scan spectrum curve was noted .the corresponding wavelength having highest absorbance is noted as λ_{max}.

1.3. Standard Calibration curve of Paracetamol in 0.1N HCl solution: 100mg of Paracetamol was weighed and dissolved in 10ml methanol and then make up to a volume of 100ml with 0.1N HCl it give 1000µg/ml concentrated stock solution (working standard). From the working standard solution 10ml was diluted to 100ml with 0.1N HCl, it will give 100µg/ml concentrated solution (Dilution 1). From the dilution 1, Aliquots of 0.2,

0.4, 0.6.0.8, 1 and 1.2ml of solution were pipette out in to 10ml volumetric flask. The volume was made up to the mark with 0.1N HCl solution. These dilutions gives 2, 4, 6, 8, 10 and 12 µg/ml concentrations of Paracetamol respectively. The absorbance was measured in the UV-visible spectrophotometer at 257 nm using 0.1N HCl solution as blank and graph of concentration versus absorbance was plotted. The absorbance data for standard calibration curves are given in the results table 1.

2. Preparation of oats powder: The domestically available oats were purchased from a local store and were grinded and passed through sieve no. 40.

3. Preparation of solid dispersion using co-grinding method: 1 gram of Paracetamol was placed in a mortar and 0.25or 0.5 or 0.75 grams of oats powder was added and grinded by sprinkling a little amount of water to moisten the powder mix. The resultant dispersion was passed sophisticatedly through sieve no.40 and dried in a hot air oven at 60^0 C for 30 minutes. This dispersion equivalent to 125 mg was used to prepare Paracetamol Fast Dissolving Tablets.

4. Preparation of paracetamol fast dissolving tablets: Fast dissolving tablets of Paracetamol were prepared by direct compression method. All the ingredients (as shown in table 2) were powdered separately and passed through sieve no. 40 separately. The drug and directly compressible excipient were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order, in an inflated polyethylene pouch magnesium stearate and talc were added last and mixed for further two minutes and the tablets were compressed using 8-12 mm flat round punches to get tablets of 250 mg weight.

5. Evaluation of oral fast dissolving tablets of paracetamol

5.1. Evaluation of blends

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

5.1.1. Bulk density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

$$\mathbf{D_b} = \frac{M}{V_0}$$

Where, M is the mass of powder, V_0 is the bulk volume of the powder

5.1.2. Tapped density (D_t): It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$$\mathbf{D_t} = \frac{M}{V_1}$$

Where, M is the mass of powder, V_t is the tapped volume of the powder

5.1.3. Carr's index (%): The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$\textbf{Carr's index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

5.1.4. Hausner's ratio: Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

$$\textbf{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

5.1.5. Angle of repose (θ): It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$\theta = \tan^{-1}(h/r)$$

Where, θ is the angle of repose, h is the height in cms, r is the radius in cms

The powder mixture was allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. A value for angle of repose $\geq 40^{o}$ suggests a poorly flowing material.

5.2. Evaluation of tablets

5.2.1. Weight variation: Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

5.2.2. Friability: Friability of the tablets was checked by using Roche Friabilator. The device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution. Pre-weighed sample tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed.

5.2.3. Content uniformity test: Ten tablets were weighed and powdered, a quantity of powder equivalent to 100 mg of Paracetamol was transferred to a 100 ml volumetric flask and 10 ml methanol is added. The drug is extracted in methanol by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with 0.1N HCl and the liquid is filtered. From prepared solution take 0.1ml solution in 10ml volumetric flask and make up to mark with 0.1N HCl . The Paracetamol content was determined by measuring the absorbance at 257 nm after appropriate dilution in UV- spectrophotometer. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

5.2.4. *In-vitro* disintegration time: The *in-vitro* disintegration test was performed by placing tablet in one tube of disintegrating basket which was dipped in 1 litre of 0.1N HCl solution maintained at 37 ^{0}C and the time required for disintegration was observed. The test is repeated for total 3 tablets and average value was considered as disintegration time for the tablet.

5.2.5. *In-vitro* dissolution data: Dissolution rate studies were performed in 900 ml of 0.1N HCl solution at 37 ± 0.5 ^{0}C, using 8-station USP type-II (paddle) apparatus with paddle rotating at 50 rpm. 60 mg of Paracetamol fast dissolving tablet was placed in dissolution basket. At fixed time intervals, samples withdrawn were filtered and spectrophotometrically analyzed for the drug content at 257 nm.

$$\textbf{\% Drug dissolved} = (A_t/A_s) \times (D_s/D_t) \times 100.$$

Here, A_t – test absorbance, A_s – standard absorbance, D_s - standard dilution & D_t - test dilution.

III. Results

Table 1: Standard Calibration Graph Values of Paracetamol in 0.1N HCl Solution

Concentration (µg/ml)	Absorbance
2	0.2722
4	0.4076
6	0.5449
8	0.6917
10	0.8235
12	0.9773

Table 2: Formulation Table for Paracetamol Fast Dissolving Tables[11,12]

	Physical Mixture			Co-grinding Method		
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Paracetamol (Equivalent to 125 mg)	156.25	187.5	218.75	156.25	187.5	218.75
Micro Crystalline Cellulose	68.75	37.5	6.25	68.75	37.5	6.25
Starch	20	20	20	20	20	20
Mg.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	250	250	250	250	250	250

Table 3: Pre Compression Studies of Paracetamol Fast Dissolving Tablets

Formulation Code	**Pre compression studies*,*n=3**				
	Angle of repose (^{0})	**Bulk density (g/cc)**	**Tapped density (g/cc)**	**Carr's Index (%)**	**Hausner's Ratio**
F1	22.17	0.515	0.522	13.15	1.10
F2	31.11	0.471	0.476	16.23	1.21
F3	25.71	0.505	0.527	14.26	1.15
F4	23.31	0.522	0.519	12.36	1.09
F5	31.11	0.471	0.476	16.23	1.21
F6	25.71	0.505	0.527	14.26	1.15

Table 4: Post Compression Studies for Formulation of Fast Dissolving Tablets of Paracetamol

Formulation Code	**Post compression studies**					
	Avg. Wt (mg) (n=20)	**Thickness (mm) (n=3)**	**Hardness (kg/cm^2) (n=3)**	***%Friability**	**%Drug content (n=3)**	**Dispersion Time (sec.)**
F1	250.4	3.82	3.5	0.59	99.98	18.5
F2	252.2	3.91	3.2	0.68	100.21	30.5
F3	249.6	3.84	3.3	0.58	99.67	92
F4	248.0	3.88	3.6	0.59	100.32	29.5
F5	249.6	3.84	3.3	0.58	99.67	23.5
F6	252.2	3.91	3.2	0.68	100.21	69.5

Table 5: *In-Vitro* Dissolution Studies of Paracetamol Tablets in 0.1N HCl Solution

Time (min)	**Marketed Formulation**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0	0
5	12	13	15	17	15	21	24
10	25	24	29	29	31	45	53
15	41	38	46	49	52	69	78
20	59	54	67	71	75	94	99
25	82	71	85	93	97	99	
30	95	84	97	98	100		

Table 6: Kinetic Data for Fast Dissolving Paracetamol Tablets

FORMULATION CODE	**R^2 values**	
	ZERO ORDER	**FIRST ORDER**
Marketed Formulation	0.9907	0.8353
F1	0.9961	0.9198
F2	0.9959	0.834
F3	0.9869	0.8545
F4	0.984	0.845
F5	0.9808	0.8707
F6	0.9974	0.7842

IV. Figures

Figure 1: Standard Calibration Curve of Paracetamol in 0.1N HCl Solution

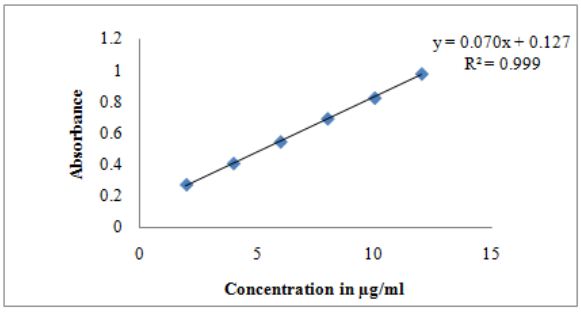
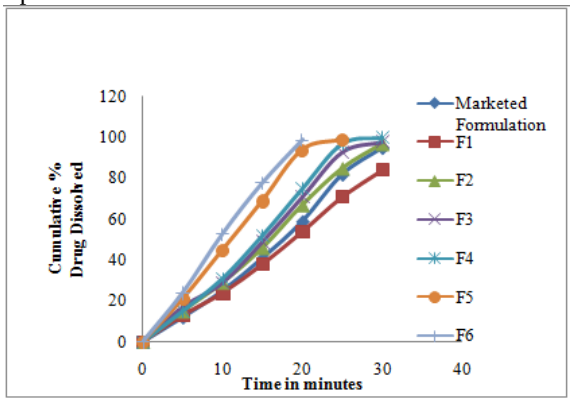


Figure 2: Comparative Dissolution Profiles for Oats Powder Used Formulations



V. Discussion

Construction of Standard calibration curve of Paracetamol in 0.1N HCl solution: The absorbance of the solution was measured at 257nm, using UV spectrometer with 0.1N HCl solution as blank. The values are shown in table no 1. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2-10 µg/ml as shown in figure 1. Standard plot of Paracetamol by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown figure 1. The standard calibration curve of Paracetamol in 0.1N HCl solution shown good correlation with regression value of 0.999.

Pre Compression studies: The prepared tablets were evaluated for their flow properties, the results for the blends of compression tablets were shown in Table 3. The bulk density and the tapped density for all formulations were found to be almost similar. The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 % and 1.09 to 1.21 respectively, indicating good flow and compressibility of the blends. The angle of repose for all the formulations was found to be 22.17 to 31.11^0 indicating passable flow.

Post Compression Studies For Formulation Of Fast Dissolving Tablets Of Paracetamol: The weight variation of tablets were within the range of ±7.5% complying with pharmacopoeia specifications of IP. The thickness of tablets was found to be between 3.82 to 3.91 mm. The hardness for different formulations was found to be between 3.2 to 3.6 kg/cm^2, indicating satisfactory mechanical strength. The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content was found to be within limits 99 to 101 %. The disintegration time for all the formulations were observed < 92 seconds.

***In-vitro* dissolution studies of Paracetamol tablets in 0.1N HCl solution:** The highest concentration of disintegrant was shown faster dissolution and lowest concentration shown slower dissolution. From the above dissolution data, it was observed that dissolution enhancement in the following order

Co-grinding > Physical Mixing

Among the formulations F6 formulation shown very fast dissolution i.e. 100% at 20^{th} minute. From the kinetic data it was observed that F6 was following zero-order kinetics. F6 formulation was formulated using banana powder as dissolving agent at 1: 0.75 ratio.

VI. Summary

Suitable analytical method based on UV-Visible spectrophotometer was developed for Paracetamol. λ_{max} of 257 nm was identified in 0.1N HCl solution. Direct compression method was established to manufacture fast dissolving tablets of Paracetamol. Fast dissolving tablets of Paracetamol were successfully prepared using banana powder using physical mixture and co-grinding method. In the present study, fast dissolving tablets were prepared by direct compression method. Evaluation parameters like hardness, friability, weight variation and drug content indicate that values were within permissible limit for all formulations. Disintegration time for all the formulations were < 92 seconds which is nearly close as marketed formulation (83 seconds), comparatively it is very less for F1 formulation. *In vitro* drug release study was carried out and based on the results; F-6 was identified as the best formulation among all the other formulations. The co-grinding used formulations has shown better release profile compared to physical mixing technique. Thus, we are able to achieve our objective of preparing fast dissolving tablets of Paracetamol with natural excipients and simple method of manufacture and enhance the dissolution of the drug.

Acknowledgements

Authors are very thankful to Lydia College of Pharmacy (Ravulapalem) & SK Health Care Pvt. Ltd (Bolaram, Hyderabad) for their great support to carry out this research work.

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