FORMULATION AND EVALUATION OF PARACETAMOL SUSTAINED RELEASE TABLETS

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Abstract

The aim of the present work is to prepare paracetamol matrix sustained release tablets wet granulation method using HPMC K100 and Ethylcellulose (F1, F2, F3 and F4) at different concentrations. To assess the flow properties of the powder blend (polymers mixed with the drug). To evaluate physical properties of the polymer matrix based tablets for weight variation, hardness, friability, thickness, drug content, uniformity, disintegration time, and in-vitro drug release Results showed good flowability and compressibility properties for all formulae. Physical properties of the tablets showed increase in polymer ratio there was decrease in friability but increase in hardness in all formulations. F2 formulation shows 99.67% of drug release for upto 12hrs. The study concluded that use of HPMC polymer producing effective stable sustained release.

Keywords: *Paracetamol, sustained release, HPMC K100, Ethylcellulose, in-vitro drug release*

1. INTRODUCTION

The basic goal of sustained release therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time, in order to reduce administration frequency and increase patient compliance [1]. Paracetamol (also known as acetaminophen) is one of the most widely prescribing analgesics and antipyretics [2] which exhibit its actions through inhibition of prostaglandin synthesis in the central nervous system via inhibition of cyclooxygenase-3 pathway [3]. Due to better tolerability and minimum chances of serious side effects, paracetamol is often drug of choice for pain and fever management in a variety of patients such as pregnant women, pediatrics, and geriatrics [4]. Moreover, it is also beneficial for patients in whom use of nonsteroidal anti-inflammatory drugs (NSAIDs) are restricted such as patient with risk of gastrointestinal complications and aspirin-sensitive asthmatic patients [4]. As per FD&A recommendation, 500–1,000 mg paracetamol maximum up to 4 gm daily is needed for the pain and fever reduction. Even though wide applicability of paracetamol in the treatment of pain and fever, its short half-life (around 2–3 hours) create problem [5]. Frequent dosing of paracetamol (i.e., four times in a day) is required to maintain steady state plasma level. To overcome this limitation of paracetamol dosing, sustained release (SR) formulation may be of great significance

2. METHODOLOGY

2.1 Standard Graph of Paracetamol

Accurately weigh the amount of 100 mg paracetamol was transferred into a 100ml volumetric flask. 20 ml of 0.1N hydrochloric acid (HCl) was added to dissolve the drug and volume was made up to 100 mL with the pH 6.8 phosphate buffer. Necessary serial dilutions were made by using this standard solution to give the different concentrations of paracetamol (5 to 50 mcg/mL) solutions. The absorbance of above solutions was recorded at λ_{max} (243 nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

Table -1. Standard Graph of Paracetamol

Conc. (mcg/mL)	Absorbance at 243nm
5	0.135
10	0.248
15	0.352
20	0.433
25	0.535
30	0.671
35	0.759
40	0.858
45	0.934
50	1.011
R^2	0.9968

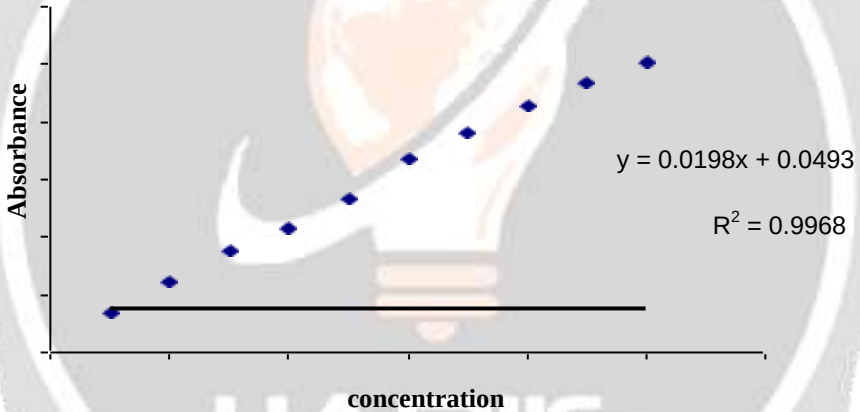

Fig-1 Standard Graph of Paracetamol

2.2 Pre-compression studies [6]

All the physical parameters namely, angle of repose, bulk density, compressibility index and Hausner's ratio were performed and the results were shown in table 2.

1. Angle of Repose:

It is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the given formula.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

2. Bulk density:

It is the ratio of total mass of powder to the bulk volume of powder. Required quantity of powder blend was transferred in 100 ml graduated cylinder and the bulk density was calculated by using the formula given below.

$$\text{Bulk Density} = \frac{\text{Weight of Powder}}{\text{Volume of Powder}}$$

Bulk Volume

3. Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder. Required quantity of powder blend was transferred in 100 ml graduated cylinder which was operated for fixed number of taps until the powder bed volume has reached a minimum Tapped density using the was calculated by formula given below.

$$\text{Tapped Density} = \frac{\text{Weight of Powder}}{\text{Tapped Volume}}$$

4. Compressibility Index:

It is a simple test to evaluate bulk and tapped density of a powder .The formula for Carr's index is as below:

$$\text{Tapped Density} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

5. Hausner's Ratio:

Hausner's Ratio is a number that is correlated to the flow ability of a powder.

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

2.3 Preparation of Paracetamol Matrix Tablets

All the matrix tablets, each containing700 mg of paracetamol were prepared by wet granulation method. Drug and the diluent (Lactose) were sifted through sieve No. 40 manually and mixed well to ensure the uniformity of premix blend. Several drug- diluent premixes were then mixed with the selected ratio of polymer(s), previously sifted through sieve No. 40, for 5 minutes. Premix blend was wet granulated with 5% w/v solution of PVP K-90 in a mortar. The wet mass was passed through No.18 sieve. The wet granules were dried at 55°C ± 5°C for 1 hour in a hot-air oven and the dried granules were sieved through No.22 sieve. These granules were blended with lubrication mixture (1% w/w magnesium stearate and 2% w/w talc) and compressed using 16 station rotary tableting machine.The formulations were tabulated in table 2.

Table- 2 Composition of Matrix Tablets Containing HPMC K100M and EC

F.Code	Paracetamol (mg)	HPMC K 100M (mg)	EC (mg)	Lactose (mg)	Magnesium stearate (mg)	Talc (mg)
F1	700	350	-	33	6	11
F2	700	700	-	33	6	11
F3	700	-	350	33	6	11
F4	700	-	700	33	6	11

2.4 Physicochemical Characterization

Thickness

Thickness of tablets was important for uniformity of tablet size. The thickness of the tablet was measured by using digital vernier caliper, twenty tablets from each batch were randomly selected and thickness was measured .Weight variation Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablet calculated.

Hardness

Hardness was measured using hardness tester, for each batch three tablet were tested.

Friability

Twenty tablets were weighed and placed in the Roche Friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted

Weight .% loss= (initial wt. of tablets – final wt. of tablets /initial wt. of tablet) x 100

Drug Content Uniformity

From each batch of prepared tablets, ten tablets will be collected randomly and powdered. The powder equivalent to 10 mg of paracetamol will be transferred in to 10 ml of volumetric flask to this 5 ml of methanol was added and then the solution will be subjected to sonication for about10 min. The solution was made up to the mark with methanol. The solution will be filtered and suitable dilutions will be prepared with pH 6.8 buffer. Same concentration of the standard solution was prepared. The drug content was estimated by recording the absorbance at 243 nm by using UV-Visible spectrophotometer.

Disintegration Test

The disintegration time is determined by using disintegration apparatus. Randomly select 6 tablets and Place them in the disintegration basket containing 900mlof phosphate buffer pH 6.8, maintaining the temperature at 37 ± 2^0C as. Note the time taken for complete disintegrate in to small particles. Perform the test in triplicate and note down the average time taken by the tablets for disintegration.

In vitro Paracetamol SR dissolution

Drug release was assessed by IP type II dissolution apparatus (basket method) at 100 rpm in 900 mL of phosphate buffer pH 6.8 upto 12 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 243 nm.

3.RESULTS & DISCUSSION

Statistical treatment of data was done accordingly. The powder characterization was determined by calculating the flow properties of different formula blend (Table 3). While the physical characterization were evaluated and the data is summarized in the table 4. The dissolution of the polymers for all formula were summarized in table 5.

Table -3 Physical Properties of Pre compression Blend :

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	25.49	0.214	0.251	14.74	1.17
F2	26.24	0.308	0.364	15.38	1.18
F3	29.05	0.276	0.322	14.28	1.16
F4	26.97	0.341	0.388	12.11	1.13

Table-4. Physical Evaluation of Matrix Tablets

F.Code	Hardness (kg/cm^2)	thickness (mm)	Weight (mg)	Drug content (%)
F1	5.50 ±0.44	3.22±0.17	119.8±1.48	98.25±1.37
F2	5.50±0.31	3.37±0.25	120.4±0.54	95.28±0.80
F3	5.58±0.40	3.14±0.80	118.6±0.41	99.12±2.47
F4	5.66±0.55	3.20±0.20	118.8±1.64	101.22±0.88

Table-5. In -Vitro Release Data of Paracetamol F1 to F4

Time (hours)	F1	F2	F3	F4
1	35.16±1.32	34.93±0.58	37.23±0.97	35.38±1.47
2	50.08±1.27	49.86±0.94	51.72±1.68	50.46±0.83
3	67.58±0.94	66.97±0.75	71.58±0.87	69.17±0.65
4	77.73±1.57	76.82±0.38	80.71±0.54	78.32±0.87

6	83.83±0.59	81.87±0.96	89.43±1.63	86.87±0.42
8	90.87±1.79	89.89±0.72	97.29±0.53	94.55±0.74
10	96.14±1.05	93.07±0.82		98.25±1.62
12	-	98.97±0.27		-

*All **v**alues represent mean cumulative percent drug released ± SD (n=3)

4. CONCLUSION

The results of dissolution studies indicated that formulation F-2, the most successful of the study, exhibited drug release pattern very close to theoretical release profile. The designed matrix tablets F-2 of Paracetamol, which release 34.93% of drug in the first hour and extend the release 98.97% upto 12 hours, can overcome the disadvantages associated with conventional tablets formulation of Paracetamol tablets. Regulated drug release in zero order kinetics attained with this formulation. Hence it can be concluded that twice a daily controlled release matrix tablet of Paracetamol having satisfactory extended release profile which may provide an increased therapeutic efficacy.

5. REFERENCES

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