e-ISSN: 2248-9126
Vol 6|Issue 2| 2016 |73-77. Print ISSN: 2248-9118

Indian Journal of Pharmaceutical Science & Research

www.ijpsrjournal.com

FORMULATION AND ENHANCEMENT OF DISSOLUTION RATE OF PARACETAMOL TABLETS EMPLOYING SELECTED BINDERS AND DISINTEGRANTS AS PER 2^2 FACTORIAL DESIGN

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ABSTRACT

Paracetamol, is a widely prescribed Non – steroidal anti inflammatory drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility, It needs enhancement in the dissolution rate in its formulation development. Binders such as Acacia and PVP K30 and use of superdisintegrant primojel and potato starch are tried for enhancing the dissolution rate of Paracetamol tablets. The objective of the present study is selection of best binder-disintegrant combination in order to enhance the dissolution rate of Paracetamol IR tablets by 2^2 factorial design. A total of four Paracetamol IR tablet formulations were prepared using selected combinations of the two factors as per 2^2 factorial design. Paracetamol tablets were prepared by wet granulation method and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K1) values were analysed by ANOVA of factorial design. The individual and combined effects of binder and disintegrant on the dissolution rate (K1) of Paracetamol tablets are highly significant ($P<0.01$). Paracetamol tablets formulated employing superdisintegrant Potato starch at a level 15% of drug content and binder PVP K30 at 2% (Fa) disintegrated rapidly within 20 seconds and gave very rapid dissolution (92.05% in 30min) fulfilling the target dissolution of NLT 80% in 30min.

Keywords: Paracetamol tablets, Factorial design, superdisintegrants (Primojel and potato starch).

INTRODUCTION

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters. These BCS class II drugs pocess challenging problems in their pharmaceutical product development process.

Paracetamol, a widely prescribed Non steroidalantiinflammatory drug (NSAID) belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. It needs enhancement in the dissolution rate in its formulation development.

Several techniques [1] such as micronisation, cyclodextrin-complexation, use of surfactants, solubilizers and super disintegrants, solid dispersion in water soluble and water dispersible carriers, microemulsions and self-emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS class II drugs. Among the various approaches, use of binders(acacia and PVP K30) and super disintegrant (primojel),potato starch [2] are simple industrially useful approaches for enhancing the dissolution rate of poorly soluble drugs in their formulation development. In the present study use of binders(acacia and PVP K30) and super disintegrant

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(Primojel), potato starch are tried for the formulation of Paracetamol IR tablets.

The objective of the present study is to formulate and enhance the dissolution rate of Paracetamol employing selected binders and disintegrants as per 2^2 factorial design to achieve NLT 80% dissolution in 30min.

EXPERIMENTAL

Materials

Paracetamol, Binders (acacia,PVP K30), lactose, Potato starch and Primojel, Talc and magnesium stearate were procured from suvarna pharmaceutical equipments, Vijayawada. commercial sources. All other materials used were of pharmacopoeial grade.

Methods

Estimation of Paracetamol

An UV Spectrophotometric method by using (LAB INDIA UV 3000) based on the measurement of absorbance at 243 nm in Phosphate buffer of pH 5.8 was used for the estimation of Paracetamol. The method was validated for linearity,Accuracy and precision. The method obeyed Beer's law in the concentration range of 1 – 10µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.92% and 1.65% respectively [3].

Formulation of Paracetamol Tablets

Paracetamol IR tablets are prepared by Wet granulation method as per 2^2 factorial design employing binders (acacia and PVP K30) and superdisintegrant (primojel) and potato starch are considered as the two factors. The two levels of the factor A (binders) are acacia and PVP K30 (2%) of drug content and the two levels of the factor B (superdisintegrants) are potatostarch(15%) and primojel (5%) of drug content. Four Paracetamol IR tablet formulations are prepared employing selected combinations of the two factors i.e., binders and superdisintegrants as per 2^2 factorial design were formulated and prepared by Wet granulation method.

Preparation of Paracetamol Tablets

Paracetamol (250 mg) tablets were prepared by Wet granulation method as per the formula given in Table 1.The required quantities of Paracetamol, binders (acacia or PVP K30) and super disintegrant (Potatostarch or Primojel) as per the formula in each case were blended thoroughly in a mortar and pestle. Talc and magnesium stearate were then added by passing through mesh no.80 and blended. The blend of ingredients was compressed directly into tablets using an SHAKTI ANISO 9001:2008 tablet punching machine employing lab press -1(GMP) using 8mm round and flat punches.

Evaluation of Tablets

All the Paracetamol tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows:

Hardness

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm2 [4, 5].

Friability

The friability of the tablets was measured in a Roche friabilator using the formula

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Drug Content

Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of Paracetamol was taken into 100 ml volumetric flask, dissolved in Phosphate buffer of pH 5.8 and the solution was filtered through Whatmann filter paper no.41. The filtrate was collected and suitably diluted with 0.1N hydrochloric acid and assayed for Paracetamol at 243 nm.

Disintegration time

Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make:Paramount) employing water as test fluid.

Dissolution Rate Study

Dissolution rate of Paracetamol tablets prepared was studied in phosphate buffer of pH 5.8 (900 ml) employing eight station dissolution rate test apparatus (LABINDIA,) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for Paracetamol at 243 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times. Each dissolution experiment was run in triplicate (n=3).

Analysis of Data

The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE_{30}) values were estimated as suggested by Khan [6,7]. Dissolution rate (K1) values were analyzed as per ANOVA of 2^2 factorial experiments.

RESULTS AND DISCUSSION

The objective of the present study is to enhance the dissolution rate of Paracetamol tablet formulation employing suerdisintigrants and binder by 2^2 Factorial design. The Paracetamol tablets as per 2^2 Factorial design

the binders and superdisintegrants are considered as two Factors. The two levels of the Factor A are Binders such as 2% acacia,2%PVP K30 of drug content, the two levels of the Factor B are disintegrants such as 15% of potato starch, 5% of Primojel of drug content. Four Paracetamol tablet formulations employing selected combinations of the two Factors binders (acacia, PVP K 30) and disintegrants (potatostach, primojel) as per 2^2 Factorial designs were prepared. The tablets were prepared by Wet granulation method as per the formula given in table .1 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K1) values were analysed as per ANOVA of 2^2 Factorial design to find out the significance of the individual and combined effects of the two Factors involved on the dissolution rate of Paracetamol tablets formulated.

Paracetamol tablets formulated employing binders & superdisintegrants:

The physical parameters of the Paracetamol tablets prepared are given in Table 2. The hardness of the tablets was in the range 4.5-5.0 kg/cm^2. Weight loss in the friability test was less than 0.95 % in all the cases. Paracetamol content of the tablets prepared was within 100±3 %. Many variations were observed in the disintegration and dissolution characteristics of the Paracetamol tablets prepared. The disintegration times were in the range 20 sec to 5min 50 sec .Paracetamol tablet formulations (F_a) & (Fab) disintegrated rapidly with in 20 sec. All other tablets disintegrated rather slowly in about 2-6 min. Paracetamol tablets prepared fulfilled the official (IP- 2014) requirements with regard to drug content, hardness, and friability and disintegration time specified for uncoated tablets.

Dissolution rate of Paracetamol tablets prepared was studied in Phosphate buffer of pH 5.8. The dissolution profiles of the tablets are shown in Fig.1 and Fig.2 and the dissolution parameters are given in Table 3. Dissolution of Paracetamol from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.952. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate (K_1) values of the tablets prepared due to formulation variables. ANOVA (Table – 4) of K_1 values indicated that the individual and combined effects of the two Factors, Potato starch, Primojel and PVP K 30,Acacia in influencing the dissolution rate of Paracetamol tablets are highly significant ($P < 0.01$) .

Higher levels of acacia and lower levels of Primojel gave low dissolution of Paracetamol tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $F_a > F_{ab} > F_1 > F_b$. Hence formulation an enhancement of dissolution rate of paracetamol tablets could be possible by 2^2 Factorial design.

Table 1. Formulae of Paracetamol Tablets Prepared, Employing Binders and superdisintegrants as Per 2^2 Factorial Design

Formulation	F_1	F_a	F_b	F_{ab}
Paracetamol	50	50	50	50
Acacia (2%)	5	-	5	-
PVP K30 (2%)	-	5	-	5
Potato Starch (15%)	37.5	37.5	-	-
Primojel (5%)	-	-	12.5	12.5
Lactose (2%)	147.5	147.5	172.5	172.5
Talc (2%)	5	5	5	5
Magnesium stearate(2%)	5	5	5	5
Total (mg)	250	250	250	250

Table 2. Physical Parameters of Paracetamol Tablets Prepared Employing, Binders and superdisintegrants as per 2^2 Factorial Design

Formulation	Hardness (Kg/Cm^2)	Friability (% Wt Loss)	Disintegration time(Min-sec)	Drug content (mg/tablet)
F_1	4.5	0.87	5-50	98.8
F_a	5.0	0.97	0-20	99.0
F_b	4.5	0.93	8-50	98.8
F_{ab}	5.0	0.92	0-22	98.7

Table 3. Dissolution Parameters of Paracetamol Tablets Prepared Employing, Binders and superdisintegrants as per 2^2 Factorial Design

Formulation	PD_{15} (%)	T_{50} (min)	T_{90} (min)	DE_{30} (%) ($\bar{x}$ ± sd)	$K_1 X 10^3$ (min^{-1}) ($\bar{x}$ ± s d)	Official specification
F_1	29.26	20	55	33.51±0.92	31±1.05	NLT 80% dissolution in 30min
F_a	61.98	8	30	58.32±0.94	56±3.61	
F_b	30.36	27	50	30.38±0.81	30.9±1.88	
F_{ab}	60.86	11	35	52.10±0.47	54±1.24	

Table 4. ANOVA of Dissolution rates (K_1) of Paracetamol tablets Prepared employing Binders and superdisintegrants as per 2^2Factorial Design

Source of variation	DF	SS	MSS	F-ratio
Total	11	73833	_	
Treatment	3	73734	24578	1.9869
Error	8	99	12.37	
PF_a	1	13480	13480	1413.0
PF_b	1	15008.3	15008.3	1132.4
PF_{ab}	1	42245.3	42245.3	3415.14

$F_{0.01}$ (3, 8) =7.59; $F_{0.01}$ (1, 8) =11.3.

Fig 1. Dissolution Profiles of Paracetamol Tablets Prepared Employing Binders and superdisintegrants as per 2^2 Factorial Design

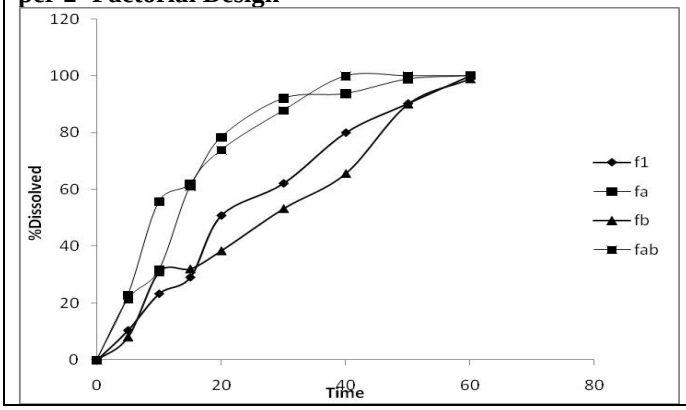
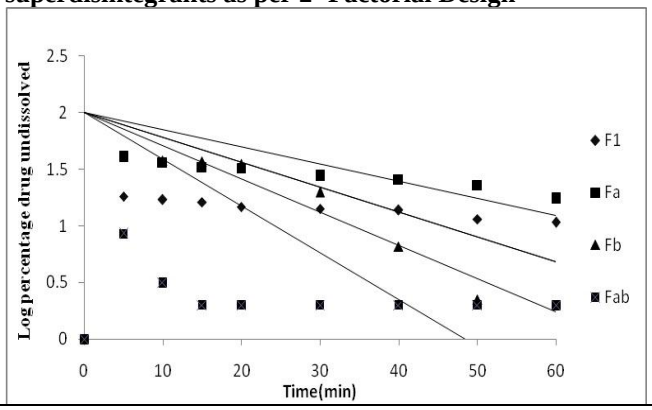


Fig 2. First order Dissolution Profiles of Paracetamol Tablets Prepared Employing Binders and superdisintegrants as per 2^2 Factorial Design



CONCLUSIONS

- The individual and combined effects of binders (acacia and PVP K30) and superdisintegrant (potato starch or Primojel) on the dissolution rate (K1) of paracetamol tablets are highly significant (P<0.01).
- Paracetamol tablets formulated employing superdisintegrant Potato starch at a level 15% of drug content and binder PVP K30 at 2% (Fa) disintegrated rapidly within 20 seconds and gave very rapid dissolution (92.05% in 30min) fulfilling the target dissolution of NLT 80% in 30min.
- The results indicated that binder PVP K30 (2%) of drug content and superdisintegrant (Potato starch) at a level of 15% of drug content are the best binder-disintegrant combinations for formulation of paracetamol IR tablets to enhance the dissolution rate of paracetamol.
- The increasing order of dissolution rate ($_{K1}$) observed with various formulations was $F_a > F_{ab} > F_1 > F_b$.
- Hence formulation of paracetamol tablets with selected combinations of binders and disintegrants could be used to enhance the dissolution rate by 2^2 Factorial design.

ACKNOWLEDGEMENT

I sincerely thank my college chairman Sri N.Seshareddygaru and Principal Dr.K.Ravishankargaru for providing me all the necessary facilities for making project success.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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