Research Article

Available online at www.JGTPS.com

ISSN: 2230-7346
Journal of Global Trends in Pharmaceutical Sciences
Volume 4, Issue 4, pp -1329-1334, October-December 2013

PREPARATION AND EVALUATION OF FAST DISSOLVING TABLETS OF PARACETAMOL EMPLOYING SUPERDISINTEGRANTS

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Journal of Global Trends in Pharmaceutical Sciences

ABSTRACT

Fast dissolving tablets (FDTs) are novel types of tablets that dissolve / disintegrate / disperse in saliva within few seconds without water. Paracetamol is a widely prescribed antipyretic and analgesic drug for all age groups. Several types of paracetamol products in the form of tablets, dispersible tablets, suspensions, syrups and FDTs are available commercially. The objective of the study is to formulate and evaluate FDTs of paracetamol employing three known superdisintegrants namely Crospovidone, Croscarmellose sodium and Primojel and one new coprocessed excipient namely Pregelatinised starch-PEG 1500- Aerosil. In each case three concentrations of superdisintegrant(2, 4 and 5 %) were used and the tablets were prepared by wet granulation method. The prepared FDTs were evaluated for drug content , hardness , friability, disintegration time , wetting time , moisture absorption and dissolution rate.

All the FDTs prepared disintegrated within 2 min 50 sec. Among the four superdisintegrantstested,Crospovidone and Croscarmellose sodium gave rapid disintegration of the tablets.FDTs formulated employing 5% Crospovidone (PF3) and 5 % Croscarmellose sodium (PF7)disintegrated within 21 and 28 sec and the wetting time of these tablets was 5 and 8 secrespectively. Water absorption ratio (%) of these tablets was 96.64 % and 74.97 respectively. All the FDTs prepared gave rapid dissolution of paracetamol. The dissolution rate ofparacetamol was increased as the concentration of superdisintegrant was increased in eachcase. At 5 % concentration the increasing order of dissolution rate (K_1) observed withvarious superdisintegrants was Crospovidone (PF3) >Croscarmellose sodium (PF7) >PGS-PEG-Aerosil coprocessed excipient (PF15) > Primojel (PF11).FDTs formulatedemploying Crospovidone , Croscarmellose sodium and PGS-PEG-Aerosil coprocessedexcipient at 5 % concentration gave more than 95 % dissolution in 30 min fulfilling theofficial dissolution rate specification of NLT 80 % in 30 min prescribed for paracetamol tablets. PVP as binder gave rapiddisintegration and dissolution rates when compared to acacia. FDTs formulated using 5%Crospovidone (PF 3) and 5 % Croscarmellose sodium (PF 7) gave rapid and higher dissolution of paracetamol than Crocin Advance, a commercial Immediate Release (IR) tablet. The new coprocessed excipient, Pregelatinised starch- PEG-Aerosil is comparable to the known superdisintegrants for formulation of FDTs.

Key words: Fast dissolving tablets, Paracetamol, Superdisintegrants, Wet granulation

INTRODUCTION

Oral route is the most preferred route for administration of various drugs because it is regarded as safest, most convenient and economical route[1]. Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/ diets have difficulties swallowing these dosage forms[2]. To overcome these problems, Fast Dissolving Tablets (FDTs) have been developed as innovative drug delivery systems. FDTs are novel types of tablets that dissolve/ disintegrate/disperse in saliva within few seconds without water.[3]Fast dissolving drug delivery systems (FDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and at the same time, offer added advantages over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. Currently these tablets are available in the market for treating many

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disease conditions like hypertension, migraine, dysphasia, nausea, vomiting, Parkinson's disease, schizophrenia and pediatric emergency[4-8].

(USFDA) defined FDTs as " A solid dosage form containing medicinal substances or active ingredients which disintegrate rapidly within a few seconds when placed up on tongue.FDTs can be prepared by various conventional methods like direct compression, wet granulation, melt granulation, moulding, spray drying,freeze drying, sublimation and by addition of superdisintegrants. FDTs disintegrate and / or dissolve rapidly in the saliva without need for water, releasing the drug. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[5].

Paracetamol is a widely prescribed antipyretic and analgesic drug for all age groups. Several types of paracetamol products in the form of tablets, dispersible tablets, suspensions, syrups and FDTs are available commercially. The objective of the present study is to formulate and evaluate fast dissolving tablets (FDTs) of paracetamol employing three known superdisintegrants namely Crospovidone, Croscarmellose sodium and Primojel and a new Coprocessed excipient namely Pregelatinised starch-PEG 1500-Aerosil (PGS-PEG-Aerosil). In each case three concentrations of superdisintegrants (2, 4,and 5%) were used and the tablets were prepared by wet granulation method and were evaluated.

EXPERIMENTAL

Materials:

Paracetamol was a gift sample from M/s Eisai Pharma technology Pvt. Ltd., Parawada, Visakhapatnam. Crospovidone, Croscarmellose sodium and Primojel were gift samples from M/s Natco Pharma, Hyderabad. Lactose, PVP K-30, PEG 1500, Rice starch, Aerosil, talc and magnesium stearate were procured from commercial sources. PGS-PEG-Aerosil coprocessed excipient was prepared in the laboratory. All other materials used were of pharmacopoeial grade.

Methods:

Estimation of Paracetamol:

An U.V spectrophotometric method based on the measurement of absorbance at 253 nm in phosphate buffer oh p^H 5.8 was used for the estimation of paracetamol. The method obeyed Beer's law in the concentration range 0 - 10 µg /ml. When a standard drug solution was assayed repeatedly (n=6), the accuracy and precision were found to be 0.8 % and 1.2% respectively.

Preparation of PGS-PEG-Aerosil Coprocessed Excipient:

Rice starch (15 parts) and PEG 1500 (5 parts) and Aerosil (0.4 parts) were dispersed in 40 parts of water to form smooth slurry. Purified water (40 parts) was taken in a separate beaker and heated to boiling. Starch-PEG-Aerosil slurry was added to boiling water while stirring. Stirring and heating was continued for 15 to 20 minutes to form a thick mass. To the mass formed, acetone (40 parts) was added and mixed thoroughly to remove the water in the product formed. The product formed was collected by filtration and further dried at 85^{o}C until dry. The dried product was grinded and sized to obtain -36+80 mesh (302.5 µm) sized particles.

Preparation of Paracetamol FDTs:

Fast dissolving tablets of paracetamol were prepared by wet granulation method employing various superdisintegrants as per the formulae given in Table 1.

Paracetamol, lactose and PVP were blended thoroughly in a dry mortar and granulated using water (q.s) as granulating fluid. The wet mass formed was pressed through mesh no: 16. The wet granules were dried at 60 ^{0} C for 1 hour. The dried granules were again passed through mesh no: 16 to break the aggregates formed and to obtain discrete granules. Superdisintegrant, talc, magnesium stearate and aerosil were passed through mesh no: 80 and collected on to the bed of tablet granulations and mixed.

The tablet granulations were blended thoroughly in a closed polyethene bag and compressed into 250 mg tablets using RIMEK tablet punching machine employing 9mm flat punches.

Evaluation of Fast Dissolving Tablets Prepared:

Uniformity of Weight[9]:

The weights were determined by using Shimadzu balance (Model ATY 224).
Weight control is based on a sample of 20 tablets.

Tablet Hardness[10]:

The hardness of prepared tablets were determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Tablet Friability[11]:

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

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

Drug Content[12]:

Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20mg of Paracetamol was taken into 100 ml volumetric flask, dissolved in phosphate buffer of pH 5.8 and the solution was filtered through whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 5.8. The drug content was determined at 253 nm.

Disintegration test[12]:

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

Wetting Time[13]:

The wetting time of the tablets was measured as follows. Five circular tissuepapers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 ml of water-containing amaranth a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Water Absorption Ratio[14]:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. Atablet was put on the tissue paper and allowed to completely wet. The wetted tablet was thenweighed. Water absorption ratio, R was determined using following equation.

$R = 100 \times (Wa - Wb)/Wa$

Where, Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption.

Dissolution Rate Study:

Dissolution rate of paracetamol tablets prepared was studied in phosphate buffer of p^H 5.8 (900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DISSO 8000) 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 253 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. Each dissolution experiment is run in tripilicate (n=3).

RESULTS AND DISCUSSION

Paracetamol FDTs were formulated employing four superdisintegrants namely Crospovidone, Croscarmellose sodium, Primojel and PGS-PEG-Aerosil coprocessed excipient. In each case three different concentrations of superdisintegrant(2, 4, 5 %) were used. The tablets were prepared by wet granulation method as per the formulae given in Table 1 and evaluated for various physical parameters and dissolution rate. The physical parameters of the paracetamol FDTs prepared are given in Table 2. The hardness of the tablets was in the range 4.5-5.5 kg/cm^2. Percent weight loss in the friability test was less than 0.70 % in all the cases. Drug content of the tablets prepared was within 100±3 % of the labeled claim.

All the FDTs prepared disintegrated within 2 min 50 sec. Among the four superdisintegrants tested. Crospovidone and Croscarmellose sodium gave rapid disintegration of the tablets.

FDTs formulated employing 5% Crospovidone (PF3) and 5 % Croscarmellose sodium (PF7) disintegrated within 21 and 28 sec and the wetting time of these tablets were 5 and 8 sec respectively. Water absorption ratio (%) of these tablets was 96.64 % and 74.97 % respectively. The dissolution rate of paracetamol from the FDTs prepared was studied in phosphate buffer of P^H 5.8 as prescribed in IP 2010. All the FDTs prepared gave rapid dissolution of paracetamol. Paracetamol dissolution from the FDTs prepared followed first order kinetics with coefficient of determination (R^2) values greater than 0.950 in all the cases. The first order dissolution rate constants (K_1) were calculated from the slope of the first order linear plots. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[15]. The dissolution parameters estimated are summarized in Table 3. The dissolution rate of paracetamol was increased as the concentration of superdisintegrant was increased in each case. At 5 % concentration the increasing order of dissolution rate (K_1) observed with various superdisintegrants was Crospovidone (PF3) >Croscarmellose sodium (PF7) > PGS-PEG-Aerosil coprocessed excipient (PF15) > Primojel (PF11).

The same increasing order was also observed based on DE_{30} values. IP 2010 prescribed a dissolution rate of NLT 80 % in 30 min for paracetamol tablets. FDTs formulated employing Crospovidone, Croscarmellose sodium and PGS-PEG-Aerosil coprocessed excipient at 5 % concentration gave more than 95 % dissolution in 30 min fulfilling the official dissolution rate specification. PVP as binder gave rapid disintegration and dissolution rates when compared to acacia. FDTs formulated using 5% Crospovidone (PF 3) and 5 % Croscarmellose sodium (PF 7) gave rapid and higher dissolution of paracetamol than Crocin Advance, a commercial Immediate Release (IR) tablet (Fig 1). The new coprocessed excipient, Pregelatinised starch- PEG-Aerosil is comparable to the known superdisintegrants for formulation of FDTs.

CONCLUSIONS

1) All the FDTs prepared disintegrated within 2 min 50 sec.
2) Among the four superdisintegrants tested, Crospovidone and Croscarmellose sodium gave rapid disintegration of the tablets.
3) FDTs formulated employing 5% Crospovidone (PF3) and 5 % Croscarmellose sodium (PF7) disintegrated within 21 and 28 sec and the wetting time of these tablets were 5 and 8 sec respectively. Water absorption ratio (%) of these tablets was 96.64 % and 74.97 respectively
4) All the FDTs prepared gave rapid dissolution of paracetamol. The dissolution rate of paracetamol was increased as the concentration of superdisintegrant was increased in each case.
5) At 5 % concentration the increasing order of dissolution rate (K_1) observed with various super disintegrants was Crospovidone (PF3) >Croscarmellose sodium (PF7) >PGS-PEG-Aerosil coprocessed excipient (PF15) > Primojel (PF11).
6) FDTs formulated employing Crospovidone ,Croscarmellose sodium and PGS-PEG-Aerosil coprocessedexcipient at 5 % concentration gave more than 95 % dissolution in 30 min fulfilling the official dissolution rate specification of paracetamol tablets.
7) PVP as binder gave rapid disintegration and dissolution rates when compared to acacia.
8) FDTs formulated using 5% Crospovidone (PF 3) and 5 % Croscarmellose sodium (PF 7) gave rapid and higher dissolution of paracetamol than Crocin Advance, a commercial Immediate Release (IR) tablet.
9) The new coprocessed excipient, Pregelatinised starch- PEG-Aerosil is comparable to the known superdisintegrants for formulation of FDTs.

Table 1: Formulae of Fast Dissolving Tablets of Paracetamol Prepared

Ingredient (mg / tablet)	Formulation															
	PF 1	**PF 2**	**PF 3**	**PF 4**	**PF 5**	**PF 6**	**PF 7**	**PF 8**	**PF 9**	**PF 10**	**PF 11**	**PF 12**	**PF 13**	**PF 14**	**PF 15**	**PF 16**
Paracetamol	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120
Crospovidone	5	10	12.5	12.5	-	-	-	-	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	5	10	12.5	12.5	-	-	-	-	-	-	-	-
Primojel	-	-	-	-	-	-	-	-	5	10	12.5	12.5	-	-	-	-
PGS-PEG-Aerosil coprocessed excipient	-	-	-	-	-	-	-	-	-	-	-	-	5	10	12.5	12.5
PVP K-30	5	5	5	-	5	5	5	-	5	5	5	-	5	5	5	-
Acacia	-	-	-	5	-	-	-	5	-	-	-	5	-	-	-	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Lactose	105	100	97.5	97.5	105	100	97.5	97.5	105	100	97.5	97.5	105	100	97.5	97.5
Total weight	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250

Table 2: Physical Parameters of Paracetamol Tablets Prepared

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration time (min-sec)	Drug content (mg/tablet)	Wetting time (Sec)	Water absorption ratio (%)
PF 1	4.7	0.68	1 -30	124.69	30	50.94
PF 2	5	0.64	1-12	125.40	15	53.70
PF 3	4.5	0.54	0-21	123.84	5	96.64
PF 4	5.5	0.60	2-18	124.62	62	19.99
PF 5	4.7	0.40	1 – 20	122.28	40	46.13
PF 6	4.5	0.45	1 – 15	118.32	30	63.08
PF 7	4.0	0.34	0-28	118.39	8	74.97
PF 8	5.0	0.45	2 – 30	123.12	44	19.90
PF 9	5.5	0.62	2 -50	117.54	252	17.17
PF 10	5.5	0.67	1 – 2	118.33	72	38.99
PF 11	5.5	0.36	1-55	116.76	185	23.39
PF 12	5.0	0.27	2-2	114.36	140	23.44
PF 13	5.0	0.48	2 – 12	118.39	82	22.12
PF 14	5.0	0.34	2 -2	122.28	52	32.89
PF 15	4.5	0.70	1 – 30	126.24	40	45.12
PF 16	5.5	0.31	2-0	116.82	37	39.09
Crocin Advance (IR Tablets)	4.5	0.13	2 -0	495.03	150	58.81

Table 3: Dissolution Parameters of Paracetamol Tablets Prepared

Formulation	Superdisintegrant (% used)	Dissolution Parameter			
		PD_{10} (%)	DE_{30} (%)	T_{50} (min)	$K_1 \times 10^2$ (min)
PF 1	Crospovidone (2)	41.58	55.12	17	4.60
PF 2	Crospovidone (4)	60.65	64.50	7.5	8.29
PF 3	Crospovidone(5)	68.53	75.56	4.5	11.97
PF 4	Crospovidone(5)	35	46.01	16	3.68
PF 5	Croscarmellose(2)	45.36	54.76	12	5.06
PF 6	Croscarmellose(4)	49.80	55.34	11	5.52
PF 7	Croscarmellose(5)	63.11	67.38	5	9.21
PF 8	Croscarmellose(5)	41.90	48.85	14.5	4.60
PF 9	Primojel(2)	28.41	31.55	29	2.76
PF 10	Primojel(4)	69.46	63.98	4	8.29
PF 11	Primojel(5)	63.84	61.61	4.5	7.36
PF 12	Primojel(5)	76.92	68.39	4.5	7.59
PF 13	PGS-PEG-Aerosil(2)	29	42.54	17	3.68
PF 14	PGS-PEG-Aerosil(4)	41.83	49.31	13.5	4.83
PF 15	PGS-PEG-Aerosil(5)	64.58	64.28	8.5	8.75
PF 16	PGS-PEG-Aerosil(5)	43.02	52.72	13	5.29
Crocin Advance (IR Tablets)	-	57.90	65.85	7	9.21

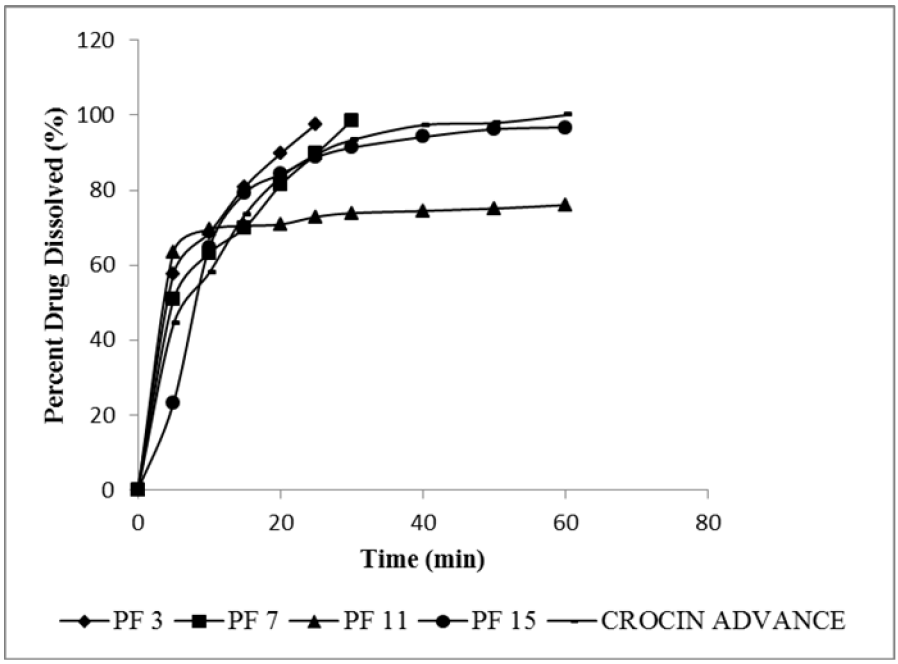

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Fig. 1: Dissolution Profiles of Paracetamol Fast Dissolving Tablets Prepared

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