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Research Article

Development and Evaluation of Mouth Dissolving Tablets of Paracetamol

Sandeep Kumar*[1], Pawan Jalwal[2]

1-Indswift, Mankumajra, Solan, Himachal Pradesh

2-Baba Mastnath University, Asthal Bohar, Rohtak

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Abstract

Paracetamol is readily absorbed from gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration. It is distributed into most body tissues. Plasma protein binding is negligible at usual therapeutic doses but increase with increase doses. The elimination half life varies from 1 to 4 hours. The absorption process occurs by passive transport. The relative bioavailability ranges from 85 % to 98 %. The apparent volume of distribution of Acetaminophen is 0.95 L/kg. A small proportion 10 to 25 % of acetaminophen is bound to plasma protein and binding is increased in plasma concentration associated with overdose.The present study involved the preparation of mouth dissolving tablet of paracetamol. The tablets were prepared by wet granulation methods. We prepared batches (F1-F18) by wet granulation and studied their release kinetic. The formulations were studied for their mouth dissoving behaviour using simulated salivery fluid; the dissolution time was noted for each formulation. Lubricated blends were characterized for physical properties like loose bulk density, tapped density, angle of repose, Carr's index, Hausner´s ratio; all blends showed satisfactory properties. Tablets were evaluated for uniformity of weight, thickness, hardness, percentage (%) friability and in vitro release studies.

Keywords: - : mouth dissolving tablet, Carr's index, Hausner´s ratio, angle of repose etc.

INTRODUCTION

Acetaminophen is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX - 1 and COX - 2, enzymes involved in prostaglandin (PG) synthesis. Unlike NSAIDS, Acetaminophen does not inhibit cyclooxygenase in peripheral anti-inflammatory affects. While aspirin acts as irreversible inhibitors of COX and directly blocks the enzymes active site, studies have found that acetaminophen indirectly blocks COX and that this blockage is ineffective in the presence of peroxides. This might explain why acetaminophen is effective in the central nervous system & in endothelial cells but not in platelets and immune cells which have high level of peroxides. Studies also report data suggesting that acetaminophen selectively blocks variants of COX enzyme that is different from the known variants COX - 1 and COX - 2. This enzyme is now referred to as COX - 3. Its exact mechanism of action is still poorly understood but future research may provide further insight into how it works. It has melting point 168-171 °C. The wavelength of Paracetamol is 247 nm according to IP standards, 243 nm (BP standards), 257 nm (USP standard). The chemical formula of Paracetamol is C8H9NO2 having molecular weight 151.1626 g/mol. The IUPAC name of Paracetamol is 4 – Hydroxyacetanilide; N – (4 - Hydroxyphenyl) acetamide.

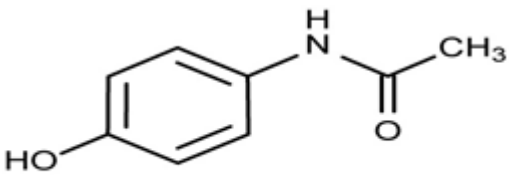

Figure 1: Structure of Paracetamol

Paracetamol is readily absorbed from gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration. It is distributed into most body tissues. Plasma protein binding is negligible at usual therapeutic doses but increase with increase doses. The elimination half life varies from 1 to 4 hours. The absorption process occurs by passive transport. The relative bioavailability ranges from 85 % to 98 %. The apparent volume of distribution of Acetaminophen is 0.95 L/kg. A small proportion 10 to 25 % of acetaminophen is bound to plasma protein and binding is increased in plasma concentration associated with overdose. Paracetamol is metabolized in liver. Approximately 90 to 95 % of dose

is metabolized in liver via cytochrome P450 enzyme pathways (primarily by conjucation with glucuronic acid, sulfuric acid andcysteine). An intermediate metabolite is hepatotoxic and most linkely nephrotoxic and can accumulate after primary metabolic pathways have been saturated. Oxidation via cytochrome P450 dependent isoenzymes CYP 2 E1 & CYP1A2 & CYP3A4. The reactive intermediate metabolite conjucates with glutathione and further metabolized to form cysteine and mercapturic acid conjugates.

Materials and Methods

Paracetamol was gifted from Shri Krishna Pharmaceutical. Cross carmellose sodium and sodium starch glycollate were purchased from Dvm international. Microcrystalline cellulose was purchased from Mingtai chemicals co. Ltd. Sucralose BP was purchased from M.B. Sugar. Ethyl cellulose was purchased from Asha cellulose. Peppermint Flavour was purchased from K.P. Manish Global Ingerdients Pvt Ltd. All other excipients are purchased from different suppliers. **Experimental methods**

Formulation development of mouth dissolving tablet of Paracetamol:

The composition of different formulations of mouth dissoving tablet of Paracetamol was shown in table 1 and 4. The ingredients were weighted accurately and mix thoroughly.

Selection of manufacturing processes:

Formulation batches were prepared using wet granulation method and their release profiles were compared to select the manufacturing process for further studies. Wet granulation method is used because of coalescing of particles which results in blend uniformity. A wide variety of powder materials can be processed into a uniform mix with improved flow. Dust and segregation tendencies are reduced**.**

Table 1: Formulation of trial batches from F1 – F4

Ingredients	F-1(Mg /tab)	F-2	F-3	F-4
PCM	500	325	500	500
Mannitol	140	352	132	155.125
MCC	-	-	-	30.125
SSG	120 (15%)	-	-	-
Crosspovidone	-	45(7.5 %)	-	-
Cross Carmellose Sodium	-	-	60 (1 %)	27 (4%)
Ammonium glycyrrizin	-	-	4 (0.5 %)	3.375 (0.5 %)
Sucralose	-	6 (1.5 %)	-	6.75 (1%)
Aspartame	-	-	-	-
Eudragit 100	-	-	12 (1.5 %)	20.25 (3.0 %)
PVP K-30	24 (1.5 %)	9 (1.5 %)	-	-
Water	80 ml	50 ml	15:10 water::Ethanol	15 :10 water: ethanol with 0.2 % citric acid
Extragranular	SSG			13.5
Crosspovidone	-	45 (7.5 %)	60 (7.5 %)	13.5
Aspartame	4 (0.5%)	-	16 (2 %)	13.5 (2 %)
Sucralose	-	6 (1%)	-	-
Talc	4 (0.5%)	3 (0.5 %)	4 (0.5 %)	3.375 (0.5 %)
Mg. Stearate	4 (0.5%)	3 (0.5 %)	4 (0.5 %)	6.75 (1%)
Strawberry	4 (0.5%)	3 (0.5 %)	4 (.5 %)	3.375 0.5 %
Menthol	-	3 (0.5 %)	4 1 (0.5 %)	3.375 (0.5 %)
Total wt.	800	800	800	800

Table 2: Formulation of trial batches from 5 – 10

Ingredients	F 5(Mg/tab)	F 6 (Mg/tab)	F - 7	F - 8	F - 9	F - 10
Paracetamol	500	500	500	500	500	500

Cross Carmellose Sodium	-------	10 (1.48%)	10			10.36 (1.48%)
PVP K-30 (3 %)	20.25	10 (1.48%)	6.75 (1 %)	3.375 (0.5 %)	3.5 (0.5%)	7 (1 %)
Water		W-10 ml	W-12 ml			W - 20 ml (1st Gran.)
Ethyl cellulose	---	2nd granulation	2nd time	16.87 (2.5 %)	17.5 (2.5 %)	17.5 (2.5 %) 2nd gran.
Mannitol	124.25	152.115	120.4775	155.9425	136.125	130.875
Micro Crystalline Cellulose	36.875	29.865	15.835	31	36.125	30.875
Cross Carmelose Na (3 %)	20.25	10.25 (1.52 %)	10.25 (1.52%)	13.5 (2 %)	14 (2 %)	10.64 (1.52%)
Sucralose (1 %)	6.75	6.75	----------	----------	----------	----------
Eudragit E-100	---------	20.25 (3%)	33.75 (5 %)	----------	----------	----------
Ammonium glycyrrhizin (0.5 %)	3.375	3.375	3.375	3.375	3.5	3.5
Citric acid	------	1.35 (0.2%)	3.375 (0.5%)	----------	3.5	3.5
Ethanol : Water	W - 22 ml	12 E : 8 W	10 : 18 (more wet)	----------	----------	-------
DCM : IPA	--------	----------	----------	10 ml : 10 ml (20)	1 : 1 (20 ml)	20 ml
Sodium Starch Glycolate (0.75 %)		5.0625	5.0625 (0.75%)	5.0625	7 (1 %)	7 (1 %)
EXTRAGRANULAR						
SSG (0.75 %)	10.5	5.0625	10.125 (1.5%)	10.125 (1.5 %)	10.5 (1.5%)	10.5 (1.5 %)
Cros povidone (1.5 %)	10.5	10.5	20.25 (3 %)	20.25(3%)	21 (3%)	21 (3%)
Talc (0.5 %)	3.375	3.375	3.375	3.375	3.5	3.5
Magnesium stearate(1 %)	6.75	6.75	6.75	6.75	7	7
Aspartame (2 %)	13.5	13.5	13.5	13.5	21 (3 %)	21 (3 %)
Sucralose	--------	---------	6.75(1 %)	6.75	5.25(0.75 %)	5.25 (0.75 %)
Manthol (0.5 %)	3.375	3.375	3.375	3.375	3.5	3.5

Strawbeery (0.5 %)	3.375	3.375	3.375	3.375	3.5	3.5
Glycyrrhizin (0.5 %)	----------	3.375	3.375	3.375	3.5	3.5
Total wt.	800	800	800	800	800	800

Table 3: Formulation of trial batches from 11 – 13

Ingredients	**Trial -11**	**Trial -12**	**Trial-13**
PCM	500	500	500
Cross carmellose Na	10.73 (1.48 %)	10.73	10.36
PVP K-30	(1%)7.25	7.25	7
Water	10 ml	10 ml	10 ml
2nd granulation			
PCM granules	**517.98**	**517.98**	**520.86**
Mannitol	105.143	101.52	114.95
MCC	30.107	30.10	21.95
CCNa	15.95 (2.2%)	15.95	10.64
Aspartame	7.25 (1%)	7.25	10.5 (1.5 %)
Glycyrrhizin	3.625 (0.5%)	3.625	3.5
Ethyl cellulose	18.12(2.5%)	18.12	17.5
Nacl	5.8 (0.8%)	-----	---------
SSG	7.25 (1%)	7.25	7
Citric acid	3.62 (0.5%)	3.625	3.5
DCM : IPA	20 ml	20 ml	20 ml
Sodium bicarbonate extragranular	------	5.8 Chitosan-3.62 (.5 %)	3.5
SSG	10.875 (1.5 %)	10.87	10.5
Crosspovidone	21.75 (3%)	21.75	21
Talc	3.62 (0.5%)	3.62	3.5
Mg. stearate	7.25 (1%)	7.25	7
Aspartame	21.75 (3%)	21.75	21
Sucralose	5.43 (0.75 %)	5.43	5.6
Manthol	3.62 (0.5%)	3.62	3.5
Strawberry	3.62 (0.5%)	----------	----------

Glycyrrhizin	3.62 (0.5%)	3.62	3.5
Pipermint flavour	3.62(0.5%)	7.25	7
Total wt.	800	800	800

Table 4: Formulation of trial batches from 14 – 18

Ingredients	Trial14(Mg/tab)	Trial-15	Trial-16	F – 17 final formulation	F – 18 final formulation
PCM	500	325	500	325	500
Cross Carmellose Na (1.48 %)	10.36	--------	-------	------	-------
PVP K-30 (1 %)	7	2.510 (0.467 %)	3.846 (0.466 %)	2.48 (0.465%)	3.83(0.465 %)
Aspartame (1.5 %)	10.5	-------	-----	------	------
Water	7 ml	------	----------	--------	------
	2nd granulation	----	------	-----	-----
Paracetamol granules	517.367				
Ethyl cellulose (2.5%)	17.5	12.50(2.3%)	19.23(2.33 %)	12.44 (2.32%)	19.18(2.32 %)
mannitol	120.2	265	-------	265	-------
MCC	20.2	----------	----------	------	-------
Cross Carmelose Na (1.52 %)	10.64	----------	----------	------	-------
Aspartame (2%)	14	----------	----------	----------	----------
Ammonium glycyrrhizin (0.5%)	3.5	----------	----------	----------	----------
Nacl (1 %)	7	----------	----------	----------	
DCM : IPA	20 ml	33 : 16 ml	33 : 16 ml	33 : 16 ml	33 : 16 ml

Strawberry (1%)	7	----------	----------		------
SSG (1 %) Extragranular	7	----------	--------		-------
SSG (2 %)	14	----------	-------	-----	
MCC	---------	150.75	174.244	116.17	170.03
Cross povidone (3%)	21	----------	---------		-------
CCNa	----------	15 (2.80 %)	23.076 (2.79 %)	14.93	23.02 (2.79 %)
Pippermint flavour	----------	7.25(1.3 %)	11.15 (1.35 %)	7.21 (1.34%)	11.12 (1.34 %)
Talc (0.5 %)	3.5	----------	-------	-------	------
Magnesium stearate (1 %)	7	2 (0.373 %)	3.076 (0.372 %)	1.990	3.06 (0.371 %)
Aspartame (1.5%)	10.5	----------	-------	34.86 (4.23%)	34.93 (4.23 %)
Sucralose (0.8 %)	5.6	10 (1.869 %)	15.38 (1.86 %)	9.953 (1.86%)	15.34(1.86 %)
Menthol (0.5 %)	3.5	---------	------	------	------
Nacl	-------	5 (0.934 %)	7.69 (0.932 %)	4.97 (0.92%)	7.67(0.929 %)
Glycyrrhizin (0.5%)	----------	5(0.934%)	7.69 (0.932 %)	4.97 (0.92%)	7.67 (0.929 %)
Total wt.	800	800	800	800	800

Evaluation of mouth dissolving tablets

Characterization of granules prepared by selected manufacturing process for all the formulation batches

Table 5: Tapped density, Bulk density, Angle of repose, Carr's index, Hausner's ratio values of different batches blend of Paracetamol

Batch No.	Bulk Density	Tapped Density	Angle of Repose	Hausner's ratio	Carr's index
F1	0.41	0.5	40.24	1.2	18
F2	0.47	0.62	36.35	1.31	24.19

F3	0.44	0.61	38.52	1.38	1.325
F4	0.43	0.57	40.21	1.325	24.56
F5	0.42	0.51	35.25	1.214	21.42
F6	0.45	0.53	36.24	1.177	17.77
F7	0.43	0.49	38.15	1.139	13.95
F8	0.44	0.51	30.13	1.159	15.90
F9	0.43	0.50	32.15	1.162	16.27
F10	0.45	0.52	32.15	1.155	15.55
F11	0.476	0.833	36.24	1.75	42.857
F12	0.44	0.52	35.02	1.181	18.18
F13	0.401	0.454	34.21	1.135	11.674
F14	0.479	0.733	39.12	1.53	34.65
F15	0.417	0.559	30.10	1.34	25.40
F16	0.446	0.498	29.05	1.11	10.44
F17	0.467	0.502	28.91	1.07	6.97
F18	0.448	0.487	27.97	1.08	8.0

Among all the batches it was found that batches F17 and F18 exhibited acceptable flow property with respect to angle of repose, Carr's index, Hausner's ratio.

Evaluation of tablets

Hardness, Thickness, Friability, Average weight was performed for all the batches (F1 to F18) and the data are presented in Table 6.

Table 6: Results of evaluation of parameters of tablets from different batches

Batch no.	Average weight (mg)	Thickness (mm)	Friability (%)	Hardness (kps)
F1	798-807	4.5 – 4.10	27.41	6.6-6.8
F2	598-610	4.2 - 4.15	24.5	6.2-6.9
F3	799-809	5.53 -5.61	16.017	28.1-32.8 N
F4	662-674	3.28 -4.60	32.03	33-38 N
F5	662-665	3.29-4.58	30.7	34-36 N
F6	662-671	4.63-4.75	2.528	42-46 N
F7	670-684	4.11-4.34	1.77	38-54 N
F8	660-672	4.12-4.62	1.811	45-69 N

F9	692-699	4.75-4.86	1.57	51-66 N
F10	691-698	4.61-4.84	0.181	59-62 N
F11	715-727	4.80-4.86	0.69	47-82 N
F12	721-727	4.05-4.98	0.418	45-68 N
F13	698-700	4.82-4.89	0.91	55-60 N
F14	695-702	4.82-4.87	1.82	60-70 N
F15	533-537	4.13-4.58	0.671	62-72 N
F16	826-830	6.06-6.12	0.169	132-137 N
F17	535-538	4.17-4.29	0.471	64-69 N
F18	823-827	5.98-6.03	0.159	133-136 N

Parameters like Hardness, Thickness, Friability, Average weight were not found to give satisfactory results for all trials

Assay:

Weigh and powder 20 tablets. Weighed accurately a quantity of 100 mg paracetamol and 50 ml of 0.1 M NaOH, diluted with 100 ml of water, shaked for 15 minutes and add sufficient water to produce 200 ml mixed and filtered and diluted 10 ml of filtrate to 100 ml with water. To 10 ml of resulting solution added 10 ml of 0.1 M NaOH dilute to 100 ml with water and measure absorbance at about 247 nm.

Formula of assay

$$X = \frac{A_T}{A_S} \times \frac{W_S}{100} \times \frac{5}{100} \times \frac{5}{100} \times \frac{100}{W_t} \times \frac{100}{10} \times \frac{100}{10} \times \frac{\text{Potency}}{100} \times \text{Average Wt.}$$

$$= \frac{X}{\text{Claim}} \times 100 = \%\ \text{Assay}$$

Assay of Paracetamol 500 mg Tablet

$$X = \frac{0.830}{0.810} \times \frac{100}{100} \times \frac{5}{50} \times \frac{5}{50} \times \frac{100}{165} \times \frac{50}{5} \times \frac{50}{5} \times \frac{99.6}{100} \times 826$$

$$X = 510.91$$

$$= \frac{510.91}{500} \times 100 = 102.182\%$$

Assay of Paracetamol 325 mg Tablet

$$X = \frac{0.845}{0.810} \times \frac{100}{100} \times \frac{5}{50} \times \frac{5}{50} \times \frac{100}{165} \times \frac{50}{5} \times \frac{50}{5} \times \frac{99.6}{100} \times 536$$

$$X = 337.529$$

$$= \frac{337.529}{325} = 103.85\%$$

Summary

Mouth dissolving tablets of Paracetamol has been formulated having dose 325 mg and 500 mg by wet granulation method. The 18 trials batches with different ratios of excipients were taken and best formulations were selected. In final formulation F-17 and F-18, Paracetamol with excipients Cross Carmellose sodium, Micro Crystalline Cellulose, Aspartame, Sucralose, Ammonium glycyrrizin, Pipperment flavor, Strawberry, Magnesium stearate, NaCl were used. Paracetamol was granulated with binder used and after that all extragranular were added. The binders in final formulation PVP K 30 and Ethyl cellulose with solvents Dichloromethane: Isopropyl alcohol was used. All parameters of tablets evaluation like hardness, weight variation, friability, disintegration, thickness, dissolution have been checked. In two trials 12 and 13, the tablet started floating because the citric acid and base Sodium bicarbonate taken simultaneously and release CO2 to excrete bubbles that cause tablet float. Different binders were used, one is water soluble, & other is water insoluble binder. The strength of eudragit is weak. Due to weak strength of binder, the tablet has failed in friability and cracking, capping problem had overcome. So water insoluble binder ethyl cellulose has taken with PVP K 30 and had good binding strength. Many disintegrants have used like cross carmellose sodium, sodium starch glycollate, crosspovidone, etc. the concentration of disintegrants were used when the disintegration time of the formulation was high. To mask the taste of bitter Paracetamol, different sweetners like aspartame, sucralose, ammonium glycyrrhizin, & flavors like strawberry for sweet taste, peppermint flavor for mint taste, are used. The compatibility study of FTIR was done with Paracetamol: excipients showed that paracetamol is pure & it has no interaction with excipients. The melting point of paracetamol was determined. The different trials of dissolution time were noted and compared the dissolution time with one another. All the parameters for precompression, angle of repose, bulk density, hausner ratios, Carr's index and post compression parameters like hardness, disintegration, dissolution, friability were checked.

Need of Mouth Dissolving Tablet

Mouth Dissolving Tablet may be suitable for the oral delivery of drugs such as protein and peptide based therapeutics that has limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in stomach. Drug delivery in MDT may be observed in pregastric sites of highly permeable buccal and mucosal tissues of oral cavity and suitable for delivering relatively low molecular weight and highly permeable drugs. Orodispersible tablets can offer several biopharmaceutical advantages such as improved efficacy over conventional dosage forms. MDT require smaller amount of active ingredient to be effective, improved absorption profiles and better drug bioavailability than regular tablets and capsules.

Future Perspective

Mouth dissolving tablets are more widely used for treatment of allergies and asthmatic attacks since these are quickly dissolved and can help in case of emergency. The potential for such dosage forms is promising because of availability of newer and advanced technologies with strong market acceptance and increasing patient demands. Mouth dissolving tablets have better patient compliance and acceptance and improved biopharmaceutical properties, improved efficacy and better safety compared with conventional oral dosage forms.

Conclusion

Mouth dissolving tablets have always attracted scientists towards development of fancy oral drug delivery systems and important position in market encountered administration problems and contributing to betterment of patient's life. The trials F- 17 & F- 18 had good properties for MDT tablets & all parameters had suitable for mouth dissolving tablets. The aspartame was taken according to US-FDA having dose 36 mg and strawberry has been taken 0.5 % in final formulation. The 325 mg for pediatric patients and 500 mg for geriatric patients and uncooperative young patients had formulated. The % drug release & % RSD were excellent of F-17 and F-18 in comparison to other formulations. Different percent release graph of 500 mg, 325 mg, and crocin advance shows that crocin advance have less release of drug. The result of dissolution initial and dissolution stability of final formulation had same % release of drug. The final formulation disintegration time and other parameter were good in compare to other formulation. According to release kinetic model, the regression coefficient R2 value is higher in zero order kinetic as well as Higuchi kinetics. So both the models are best release kinetic model. Compare the dissolution results with crocin advance (GlaxoSmithKline) and crocin advance disintegration time was 4 minute and dissolution was poor in comparison to 500 mg & 325 mg MDT formulation. The D.T of fast dissolving tablet is less than 3 minutes but crocin D.T was four minute.

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Correspondence Address:
Sandeep Kumar
Indswift, Mankumajra, Solan, Himachal Pradesh
Email:
Phone: +91-9996886957