Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 3, 2012

Research Article

DEVELOPMENT AND EVALUATION OF PARACETAMOL TASTE MASKED ORALLY DISINTEGRATING TABLETS USING POLYMER COATING TECHNIQUE

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Received: 25 Nov 2011, Revised and Accepted: 30 Jan 2012

ABSTRACT

The purpose of this research was to mask the intensely bitter taste of paracetamol and to formulate the orally disintegrating tablets (ODTs). Taste-Masked orally disintegrating tablets of paracetamol were prepared by Flash Tab Technology. Taste masked granules of paracetamol were prepared by coating the granules of the drug using a pH-sensitive polymer Eudragit EPO in a fluidized bed coater and the coated granules were evaluated for various parameters like Bulk density, Tapped density, Compressibility index, Hausner's Ratio and Angle of Repose. Wet granulation technique was used for the preparation of the tablets using crospovidone and hydroxypropyl cellulose as disintegrants. The tablets were evaluated for post compaction parameters like thickness, friability, weight variation etc. Disintegration time of the tablets was found to be 27 sec and almost 100% drug released in 30 minutes. The taste of the formulation was found to be acceptable by analyzing the responses of the healthy human volunteers. Thus, taste-masked orally disintegrating tablets of paracetamol can be effectively prepared by a convenient wet granulation method.

Keywords: Taste masking, Orally disintegrating tablets, Polymer coating technique, Paracetamol.

INTRODUCTION

Despite tremendous advancement in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. The most popular dosage form being tablets and capsules, one important drawback of these dosage forms however is the difficulty to swallow[1]. Dysphagia is also associated with a number of medical conditions including stroke, Parkinson's disease, AIDS, head and neck radiation therapy and other neurological disorders including cerebral palsy[2-4]. Traditional tablets and capsules administered with 8oz glass of water may be inconvenient and impractical for such patients, leading to ineffective therapy[5].

The orally disintegrating tablets (ODTs) are a perfect hit for all these problems[6, 7]. Recently fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice for the reason of rapid disintegration or dissolution, self-administration even without water or chewing[8]. A major component of success in orally disintegrating tablets is good taste. If the product does not taste good, patients and physicians will find an alternative product that tastes good. ODT technology is relatively new to the pharma industry and has a significant effect on the patients of all ages. For systemic use, drug must be released from the tablets that dissolved in the fluids of the mouth, stomach and intestine and then absorbed into systemic circulation by which it shows its therapeutic effects[9]. The single most significant issue with ODT is the bitterness of the drug that can be exposed as the tablet breaks apart in the oral cavity. Skillful taste masking is needed to hide this bitterness, and combining this with the right flavor and sweetness levels will result in a superior product[10].

Paracetamol is a widely used analgesic and antipyretic drug among all age groups. Pediatric and geriatric patients are widely involved in the target population of this drug. It is very bitter in taste[11], therefore it was considered as a suitable candidate for preparing mouth dissolving tablets.

MATERIALS AND METHODS

Materials

Paracetamol was a gift sample from Sri Krishna Pharmaceuticals, Hyderabad. Aminoalkyl Methacrylate copolymer (Eudragit EPO) was purchased from Rohm Pharma Germany, Mannitol (Mannogen, SPI Pharma USA) and Advantose 100 (SPI Pharma, USA) were used as diluents. The superdisintegrants used were crospovidone (Kollidon CL, BASF South East Asia Pvt. Ltd), low substituted hydroxylpropyl cellulose (LHPC LH-21 Shin-etsu Chemical Co. Ltd, Japan) and Polyplasdone INF-10. Strawberry and Cocoa flavors were purchased from Quest International India Ltd. All reagents and solvents used in the study were of analytical grade.

Determination of Threshold Concentration of Paracetamol

The minimum concentration among a range of dilutions of a substance at which the volunteers just start feeling the bitter taste is known as the threshold concentration. A stock solution of 1600µg/ml of paracetamol was prepared by dissolving 160mg of drug in 100ml of Phosphate buffer pH5.8. Serial dilutions were made to obtain a concentration of 100-1600µg/ml. After the rating was done by panel on the scale of bitterness (0-5), the range was narrowed to 200-400µg/ml. Rating was repeated with narrowed concentrations and threshold bitterness concentration of paracetamol was determined.

Taste Masking with Polymer Coating Technique

Paracetamol granules were prepared using PVP K-30 solution as a binder and passing the wet mass through sieve of mesh no 22. The granules were dried in a rapid dryer at 60-65°C for 10-15 minutes. Fines were removed from the granules so as to facilitate the coating process by sieving through mesh no 40. These granules were coated with the coating solution as mentioned in Table1. Initial weight of the paracetamol granules was noted and during different intervals in between the coating, the weight of the coated granules was noted and the coating percentage was calculated as:

$$\text{Percentage coating} = \frac{\text{(weight of the coated granules/initial weight of the granules)}}{\times 100}$$

The coating was continued up to 10% weight gain.

Table 1: Composition of the coating solution

S.No.	Materials	Quantities (g/100 ml)
1.	Crospovidone	4.45
2.	Eudragit EPO	4.45
3.	Hydroxypropyl Cellulose	4.45
4.	Talc	0.8

Preparation of Granules by Wet Granulation and Evaluation of the Blends

The coated taste masked granules were used to prepare 250mg dose strength paracetamol orally disintegrating tablets by wet granulation technique[12]. The required quantities of the materials for granulation (Table 2) were accurately weighed and passed through sieve of mesh no 40.The materials were dry mixed uniformly. Water was used as solvent for granulation. The wet mass prepared was passed through sieve no. 16 and was dried in a rapid dryer at 60°C. Material obtained was again sieved through sieve no. 20 and subjected for evaluation of granules. The coated granules of Paracetamol were mixed uniformly in the prepared granules and flavor and lubricant were geometrically added to the blend.

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. The blends for the orally disintegrating tablets were characterized for various parameters.

Table 2: Trials Based on Wet Granulation Technique

Formulation	Granulation Step (mg/tab)							Mixing and lubrication (mg/tab)						Total Weight (mg)
	A-100	M	P -INF	K-CL	LHPC	Asp	Neo	PCM	Flavour		MS	CSD	SSF	
									Sbry	Coca				
F-1	20.0	400.0	94.0	-	-	12.0	-	268.2	5.2	-	-	-	-	800.0
F-2	-	412.2	-	70.0	25.0	10.0	-	268.2	8.0	-	4.0	2.0	-	800.0
F-3	-	591.0	-	84.0	35.0	-	0.27	268.2	15.0	-	4.0	2.0	-	1000.0
F-4	-	732.0	-	120.0	40.0	12.0	-	268.2	15.0	-	-	-	12.0	1200.0
F-5	-	698.0	-	150.0	50.0	12.0	-	268.2	15.0	-	-	-	18.0	1200.0
F-6	-	680.0	-	150.0	50.0	12.0	-	268.2	15.0	-	-	-	24.0	1200.0
F-7	-	680.0	-	150.0	50.0	12.0	-	268.2	-	15.0	-	-	24.0	1200.0

A-100 –Advantose 100; M – Mannitol; P-INF – Polyplasdone INF- 10; K-CL – Crospovidone; LHPC – Low Substituted hydroxypropyl cellulose; Asp – Aspartame; Neo – Neotame; PCM – Microencapsulated Paracetamol; MS – Magnesium Stearate; CSD – Colloidal Silicon Dioxide; SSF – Sodium Stearyl Fumarate.; Sbry – Strawberry ; Coca – Cocoa flavor

Formulation and Evaluation of Orally Disintegrating Tablets

The final blend was compressed in a rotary tablet compression machine and the tablets were tested for general appearance, size and shape, thickness, uniformity of weight, hardness and friability[13, 14]. Disintegration testing of the tablets was done in USP Disintegration Tester[15]. Tablets were assayed according to Indian Pharmacopoeia, 1996. Dissolution rate was studied using USP type II (Paddle type) apparatus at both 50 and 100 RPM to study the effect of coating on the dissolution rate at both RPMs in 900ml of phosphate buffer pH 5.8[16]. Samples were withdrawn after 10, 20, 30, 45 and 60 minutes and the dissolution profiles were compared with that of immediate release marketed preparations of Crocin and Calpol. Taste evaluation of the tablets was done by a group of 20 healthy volunteers.

Stability Studies

The tablets which passed all the pharmacopoeial, physical, dissolution, disintegration and taste evaluation tests were subjected to stability studies. Stability testing of the final drug product was carried out as mentioned in the ICH guidelines for stability testing of the drug products[17]. India being in the zone 4 of the climatic zone classification, the real time stability studies were carried out at 30±2°C and 70±5% RH. The orally dispersible tablets were subjected to the accelerated stability testing at the temperature of 40°C±2°C and 75±5% RH for 3 months. The samples were withdrawn from the stability chambers after 1 month and 3 months and studied for physical characteristics like any color change, visual defects, hardness, dissolution, disintegration and assay. The data so obtained was compared with the initial data of the tablets.

RESULTS AND DISCUSSION

It is evident from the data given in Table 3 that most of the volunteers found the concentration of 200µg/ml to be tasteless and after that the concentration of 400µg/ml was found to be slightly bitter by most of the volunteers. Therefore the concentration range was further narrowed to 200 and 400 µg/ml. 250, 300 and 350 µg/ml concentrations were further tried and majority of the volunteers found the concentrations of 250 and 300 µg/ml as tasteless and the concentration of 350 µg/ml was adjudged as slightly bitter by most number of volunteers, therefore 350 µg/ml was the minimum concentration at which majority of the volunteers just started feeling the bitter taste. Therefore, Threshold Concentration of paracetamol = 350 µg/ml.

Table 3: Determination of Threshold Concentration of Paracetamol

S. No.	Concentration (µg/ml)	No. of volunteers rating the solution as:					
		0	1	2	3	4	5
1.	100		20				
2.	200		19	1			
3.	400		2	14	4		
4.	800			10	7	3	
5.	1600				5	12	3
The concentration range was now narrowed between 200 and 400µg/ml.							
6.	250		17	3			
7.	300		13	7			
8.	350			16	2	2	

Evaluation Scale: 0 = good ; 1 = Tasteless ; 2 = Slightly Bitter ; 3 = Bitter ; 4 = Very Bitter ; 5 = Aweful.

Taste Masking With Polymer Coating Technique

Complete taste masking of paracetamol granules were observed by coating the granules with a coating solution comprising of crospovidone (4.45%w/v), Eudragit EPO (4.45%w/v), Hydroxypropyl cellulose (4.45%w/v) and Talc (0.8%w/v) in a fluidized bed coater. The methacrylate copolymer Eudragit EPO is highly suitable for taste masking, showing taste masking properties even at a low thickness.

The coated granules, which were white to off white in colour, were evaluated for different parameters and bulk characterization (Table 4).

Table 4: Evaluation of Coated Granules

S. No.	Parameter	Result
1.	Bulk density	0.477g/ml
2.	Tapped density	0.497g/ml
3.	Compressibility Index	4.024%
4.	Hausner Ratio	1.042
5.	Angle of repose	17.7°
6.	Percentage coating	7.0%w/w

The dissolution studies of the granules were carried out in phosphate buffer pH 5.8 at 100 rpm. The samples were withdrawn at different time intervals of 10, 20, 30, 45 and 60 minutes and analyzed spectrophotometrically at 244nm[18]. Table 5 shows the dissolution profile of the coated granules at 100 RPM. It was found that almost 100% of drug was released in about 30 minutes from these taste masked granules.

Coated granules were subjected for taste evaluation by the volunteers and the time for which granules remained tasteless was noted. It was found that coating remained intact for 20-25 seconds as the coated granules were observed to be tasteless for 20-25 seconds by the volunteers. The coating acted as physical barrier between the bitter drug molecules and the taste buds hence effective taste masking was achieved by coating with pH sensitive polymers.

Table 5: Dissolution profile of coated granules at 100 RPM

S. No.	Time (mins.)	Percentage Release						Mean% Release	%RSD
		Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6		
1.	10	82.4	84.9	83.2	89.7	88.3	85.6	85.7	1.8
2.	20	98.3	97.7	100.2	100.8	101.3	99.3	99.6	2.1
3.	30	99.7	98.3	102.5	100.3	99.8	100.4	100.1	0.9
4.	45	99.5	100.5	101.7	101.3	102.3	100.8	101.0	1.3
5.	60	100.2	99.8	102.1	100.5	103.1	102.5	101.4	2.1

Formulation of Orally Disintegrating Tablets

Initial trials were carried out to formulate the orally disintegrating tablets of coated paracetamol by direct compression technique. Various directly compressible excipients like Compressol S and Pharmaburst were used in the formulation development process. Polyplasdone INF-10 was used as disintegrant and Aspartame and strawberry were used as sweetener and flavoring agent respectively. Direct compression was found to be unsuitable for paracetamol ODTs as the dose of paracetamol is very high; therefore high amount of directly compressible excipients had to be used and even the problems of high disintegration time and bitter taste were still present in the trials.

Preparation of the Granules and Orally Disintegrating Tablets

Wet granulation method was also used to formulate the tablets as stated in Flash Tab technology[19] of the ODTs. Microencapsulated paracetamol granules were mixed with granulated mixture of excipients prepared by wet granulation method. Table 6 shows the results of evaluation of blends of paracetamol 250mg tablets formulation prepared by wet granulation method. During tablet production, the die filling process is based on continuous and uniform flow of the powder from the hopper to the feed frame and into the die cavity. Hence, to determine the suitability of the powder blend, the blends were characterized for various powder properties.

Table 6: Evaluation of the Blends

S. No.	Formulation Code	Bulk Characterization							
		Angle of Repose	Bulk density (gm/ml)	Tapped density(gm/ml)	Compressibility index (%)	Hausner ratio	Bulkiness (ml/gm)	Void volume (ml)	% Porosity
1.	F-1	23.2	0.505	0.598	15.552	1.184	1.98	7	15.6
2.	F-2	24.7	0.489	0.593	17.538	1.213	2.044	11	18.03
3.	F-3	21.8	0.569	0.655	13.129	1.151	1.757	7	13.208
4.	F-4	19.7	0.415	0.508	18.367	1.225	2.409	9	18.75
5.	F-5	22	0.441	0.522	15.517	1.184	2.268	11	15.493
6.	F-6	25	0.431	0.493	12.5	1.143	2.320	9	13.043
7.	F-7	24.5	0.451	0.584	22.193	1.294	2.217	14	22.807

All the parameters of the blend were found to be appropriate indicating that a fair granulation had been achieved in each formulation of wet granulation technique.

After the evaluation of the blend, compression of this blend was carried out in a rotary tablet machine at different compression pressures. Different formulations from F1 to F6 were prepared by using Polyplasdone, Crospovidone (8.75%) and Hydroxypropyl cellulose (3.2%) as superdisintegrants and mannitol as a diluent. Mannitol was selected as a diluent for ODTs as it has some sweetening value and also has a negative heat of solution which imparts a sweet and cooling effect in mouth. It also has high solubility therefore results in quick disintegration and defragmentation of the tablets[20]. Aspartame was selected as sweetener at low concentrations it is reported to reduce the bitterness of paracetamol. Table 7 displays the results of evaluation of different parameters of ODTs prepared by wet granulation method and Table 8 shows the effect of hardness on friability and disintegration time of these formulations.

It is evident from the table that the disintegration time increased as the hardness of the tablets was increased. The hardness value at which the disintegration time was less than 30 seconds and the friability was less than 1% w/w was selected.

Table 7: Evaluation of Fast Dissolving Tablets

S. No.	Parameter	Formulation Code						
		F-1	F-2	F-3	F-4	F-5	F-6	F-7
1.	Tablet Weight	800	800	1000	1200	1200	1200	1200
2.	Die/Punch	13 mm round flat punch	13 mm round flat punch	16 mm round flat punch	16 mm round flat punch	16 mm round flat punch	16 mm round flat punch	16 mm round flat punch
3.	Thickness	6.20±0.2	6.25±0.2	4.4±0.2	5.5±0.2	5.5±0.2	5.6±0.2	5.5±0.2
4.	Hardness	30	40	40	70	70	70	70
5.	Uniformity of weight	Complies	Complies	Complies	Complies	Complies	Complies	Complies
6.	Taste	Bitter	Bitter	Slight aftertaste	Acceptable	Acceptable	Acceptable	Acceptable
7.	Mouth feel	Grittiness	Grittiness	OK	OK	OK	OK	OK
8.	Processing Problems	Sticking, rough tablet surface	Sticking, rough tablet surface	Sticking, Picking	Sticking	Sticking	No	No

Table 8: Effect of hardness on Friability and Disintegration Time

S. No.	HardnessN	Disintegration time(sec) and Friability(%w/w) of different formulations													
		F-1		F-2		F-3		F-4		F-5		F-6		F-7	
		D.T	F	D.T	F	D.T	F	D.T	F	D.T	F	D.T	F	D.T	F
1.	25	68	>1 %	29	>1 %	19	>1%	17	>1%	15	>1%	14	>1%	17	>1%
2.	30	74	>1 %	34	>1 %	21	>1%	21	>1%	17	>1%	18	>1%	18	>1%
3.	40	78	>1 %	37	>1 %	25	>1%	23	>1%	19	>1%	19	>1%	21	>1%
4.	50	82	>1 %	41	>1 %	29	>1%	27	>1%	22	>1%	22	>1%	24	1.97
5.	60	88	0.97	45	1.03	36	0.95	30	1.17	25	1.22	25	1.29	26	1.41
6.	70	93	0.83	52	0.89	41	0.85	35	0.87	28	0.9	27	0.89	29	0.93
7.	80	101	0.79	61	0.81	47	0.82	41	0.83	35	0.87	34	0.83	38	0.79

The final optimized formulations i.e. F6 contained Crospovidone(12.5%), Hydroxypropyl cellulose(4.2%), aspartame(1%), sodium stearyl fumarate (2%) and the final tablet was adjusted to be 1200 mg. Disintegration time was found to be 27 seconds and friability was 0.89 % w/w. Another formulation F7, was prepared on the similar lines as that of formulation F6, only difference was in the flavor used. Cocoa flavor was used in F7 instead of strawberry flavor. When the taste masking evaluation was done by the volunteers, it was found that most of the volunteers preferred strawberry flavor over cocoa flavor. Therefore formulation F6 with strawberry flavor was selected for further dissolution and stability studies.

From the dissolution profile of the formulation, it was clear that almost 100% of the drug released in about 30 minutes (Fig.1) which was further compared with the marketed immediate release Paracetamol products. The release rate of the tablets was found to be identical with the immediate release preparations.

Bioequivalence Testing of the Formulations with Reference Standards

The dissolution profile of the formulation F-6 was compared with that of the marketed immediate release preparations of the Paracetamol and the bioequivalence was compared. From the dissolution profile of the marketed preparations (Fig.2), it was found that 100% of the drug is released in 45-60 minutes in case of Crocin tablet, whereas the complete release of the drug took some more time in case of Calpol tablets. But in case of the formulations F-6, almost 100% of the drug is released in about 30 minutes at both the RPMs 50 and 100. Therefore, in these mouth dissolving tablets, the release of the drug was slightly faster than the marketed immediate release preparations.

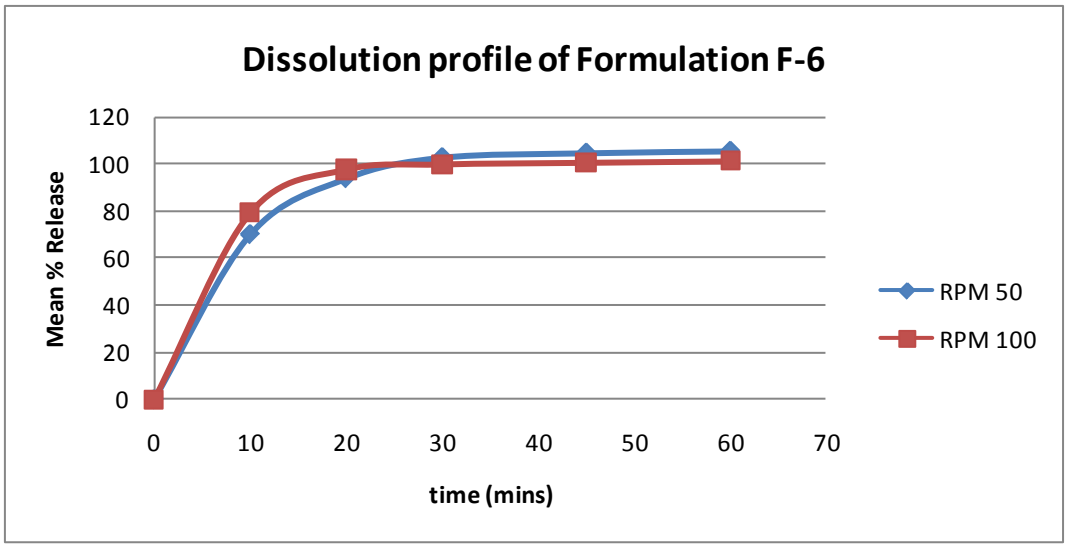
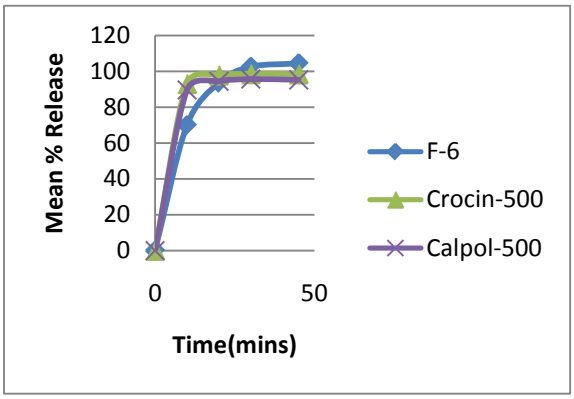
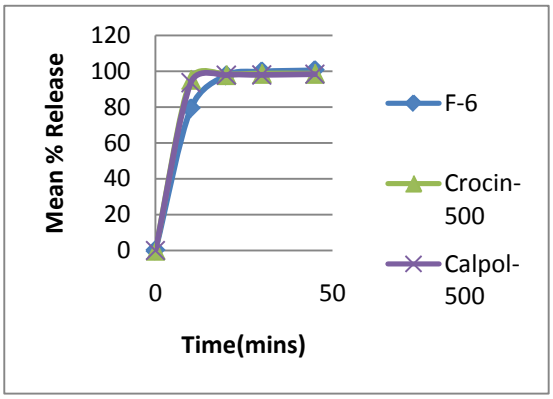


Fig. 1: Dissolution profile of formulation F6 at RPM 50 and 100



RPM 50



RPM 100

Fig. 2: Bioequivalence Testing of the Formulations with Reference Standards

Stability Studies of the Formulations

The final optimized tablets were kept in the stability chambers of 40°C/75% RH condition after proper labeling. The stability samples were withdrawn after 1 month and 3 month and evaluated to assure that no degradation or instability occurred in these formulations at the accelerated stability conditions. From the comparison of the stability data of these formulations with the initial samples, it was found that the product remained stable at such accelerated storage conditions. No color change or spotting was observed on the tablet surface of these stability samples indicating that no physical degradation was there in both the stability samples of 1 month and 3 month. Various other tests like assay, disintegration time, water absorption ratio and wetting time were also performed on these stability samples and results when compared with the initial samples suggested that there were no degradation of the product and the formulations were stable at such accelerated stability conditions. Disintegration time of the stability samples was found to be comparable to that of initial samples. Assay, water absorption ratio and wetting time[21] of the stability samples of 1 month and 3 month were almost similar to that of the initial samples. The stability data of the formulations F-6 is tabulated in the Table 9.

Table 9: Stability data of Formulation F-6

Storage Condition	Description	D.T (sec)	Assay	% Release (30 mins)	Water Absorption Ratio	Wetting Time (sec)
Initial	White round biconvexed, bevel edged uncoated tablets, plain on both sides.	27	100.64 %	102.5 %	87.09 %	12
40°C/75% RH						
1 Month	Same as initial	28	101.72 %	102.29	88.02	14
3 Month	Same as initial	31	102.69 %	100.44	88.17	16

Table 10: Dissolution profiles of Stability Samples

Stability Sample (1 Month)

S. No.	Time (mins)	Percentage Release						Mean% Release	%RSD
		Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6		
1.	10	68.97	67.80	71.02	70.43	67.80	67.80	68.97	1.2
2.	20	94.70	95.28	96.74	97.91	97.03	95.86	96.25	2.4
3.	30	100.54	102.0	104.92	104.04	101.12	101.12	102.29	1.4
4.	45	102.0	103.17	103.17	105.50	105.80	102.58	103.70	1.3
5.	60	101.71	101.12	102.29	105.50	105.21	102.87	103.12	0.9

Stability Sample (3 Months)

S. No.	Time (mins)	Percentage Release						Mean% Release	%RSD
		Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6		
1.	10	56.11	65.76	71.02	64.29	66.92	64.29	64.73	3.6
2.	20	87.38	91.48	95.57	92.35	92.64	87.38	91.13	2.8
3.	30	93.81	101.12	107.84	102.58	101.41	95.86	100.44	1.9
4.	45	97.61	104.92	106.67	105.21	102.58	97.61	102.44	2.1
5.	60	94.98	100.54	107.26	104.34	101.70	97.03	100.98	1.7

When the dissolution profile of the stability sample of the formulation F-6 was compared with the initial sample, it was observed that there was not much difference in the release pattern of the drug at different time intervals. Almost 100 % of the drug is released in 30 minutes in both the stability samples which was very much similar to the release of the drug in the initial samples.

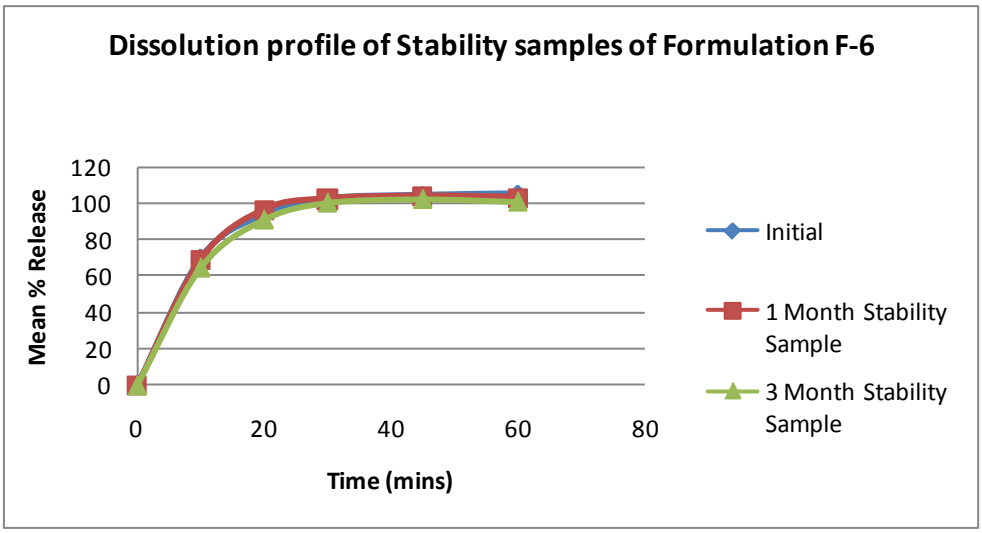


Fig. 3: Dissolution Profiles of Stability Samples of Formulation F6

From the comparison of the stability data of formulation with the initial samples (Table 10), it was found that the product remained stable at such accelerated storage conditions. No color change or spotting was observed on the tablet surface of these stability samples indicating that no physical degradation was there in both 1month and 3 months stability samples. Disintegration time of the stability samples was found to be comparable to that of initial samples. When the dissolution profile of the stability sample of the formulation was compared with the initial sample, we found that there was not much difference in the release pattern of the drug at different time intervals. Almost 100 % of the drug is released in 30 minutes in both the stability samples which was very much similar to the release of the drug in the initial samples also.

CONCLUSION

The study conclusively demonstrated complete taste masking of paracetamol and rapid disintegration and dissolution of Orally Disintegrating Tablets of Paracetamol. Coating with pH sensitive polymers Eudragit EPO and Hydroxy Methyl Cellulose effectively masked the bitter taste of paracetamol. Complete taste masking was achieved and stable mouth dissolving tablets of Paracetamol were formulated with superior organoleptic properties, excellent in vitro dispersion time and drug release almost identical to marketed preparations of Paracetamol. However, in the view of the potential utility of the formulation, stability studies were carried out at recently changed ICH conditions at 30±2°C/65±5% and 40±2°C/75±5% for 6 months[22].

ACKNOWLEDGEMENT

The authors are thankful to Mr Dinesh Singla, DGM, Formulation Research Development, Panacea Biotech Ltd, Lalru for the needy support and the guidance.

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