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Research Article

Formulation and evaluation of prednisolone sodium phosphate orally disintegrating tablets

N.Adinarayana[1]*, S.Brito Raj[1], Shrinivas gopal hukeri[2], M .Rajasekhar[3], K.Bhaskar Reddy[1], E.Mohanambal[1]

[1]Department of Pharmaceutics, Srivenkateswara College of Pharmacy, Chittoor, Andhra Pradesh, India
[2]Department of pharmaceutics, Millind institute of pharmacy, JC Nagar, Bangalore, India
[3]Department of Pharmaceutics, SRM College of Pharmacy, Chennai, Tamil Nadu, India

ABSTRACT

There is an increasing demand for more patient compliant dosage form and a novel method is the development orally disintegrating tablets which dissolve or disintegrates instantly on the patient tongue or buccal mucosa. Prednisolone is a naturally occurring glucocorticoids (hydrocortisone), it targets to corticosteroid binding globulin (it regulates Enzyme regulatory activity, Enzyme inhibitory activity and protease inhibitor activity. Used in treatment of severe inflammatory conditions including allergies, arthritis, asthma, or skin reactions.Its metabolizing enzyme is Cytochrome P450 3A4 (CYP 3A40). Hence the main objective of the study was to formulate orally disintegrating tablets of Prednisolone to achieve a better dissolution rate and further improving the bioavailability of the drug. Orally disintegrating tablets prepared by direct compression and using super disintegrate like crospovidone, croscarmellose sodium and sodium starch glycolate designate, designated as three different groups of formulation (F-1 to F-13) respectively were prepared and evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. In present work wet granulation technique was employed to prepare tablets. Microcrystalline cellulose is used as diluents. Aspartame and mannitol is used as sweetening agents. Crospovidone XL10 as disintegrant. Prednisolone Sodium Phosphate was having bitter taste and to mask the bitter taste flavoring agent like mint flavor and taste masking agents like PEG4000, Ethyl cellulose 4cps, Eudrait EPO and Eudragit L100. Post compressional parameters hardness, friability, weight variation, disintegration time, drug content and dissolution studies are studied. All three groups of formulations released the drug at faster rates than that of marketed conventional tablets of Prednisolone.

Keywords: Predinsolone; Superdisintegrants; Orally disintegrating tablets.

INTRODUCTION

Prednisolone is a naturally occurring glucocorticoids (hydrocortisone), it targets to corticosteroid binding globulin (it regulates Enzyme regulatory activity, Enzyme inhibitory activity and protease inhibitory activity. Which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states (Vyas.sp, et al). Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems. Used in treatment of severe inflammatory conditions including allergies, arthritis, asthma, or skin reactions. Various techniques can be used to formulate orally disintegrating tablets or fast dissolving tablets. Direct compression one of the techniques requires the incorporation of a superdisintegrants into the formulation the use or highly water soluble excipients to achieve fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications (Suresh Bandari et al, 2008, William.R et al, 2005, Alkire et al, 1997). The aim of purpose work was to formulate and characterization orally disintegrating tablets of Predisolone sodium phosphate for rapid dissolution of drug and absorption, which may produce the rapid onset of action in the treatment of depression and anxiety disorder. To develop and formulate Predisolone sodium phosphate orally disintegrated tablets using different concentrations of taste masking and enteric coating material. To mask the unpleasant bitter taste of the API and prepare a Orally disintegrating tablets using taste masking materials, enteric coating materials and super disintegrates. (Wehling et al,1996, Liberman.A.Herbert et al,1991)

* Corresponding Author
Email: adi_guessme@yahoo.com
Contact: +91-9030287109
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Table 1: Formulation of Prednisolone ODT (30mg) Intragranulation (mg/tab)

Ingredients	F1	F2	F3	F4	F5	F6	F7
API	42.98	42.98	42.98	42.98	42.98	42.98	42.98
Poly Ethylene Glycol 4000	__	__	__	__	40	40	42.98
Ethyl cellulose 4cps	__	__	__	__	__	__	__
Purified water	Q.S.	Q.S.	Q.S.	__	Q.S.	Q.S.	Q.S.
Ethyl cellulose	__	10	__	12	15	__	__
Isopropyl alcohol	Q.S.	Q.S.	__	__	Q.S.	Q.S.	__
Methylene chloride	__	__	__	__	Q.S.	Q.S.	__
MCC (Avicel pH101)	100	250	250	248	245	245	225
Aspartame	__	__	__	__	__	__	10
Mannozem. EZ (spray dried mannitol)	244.02	__	__	__	__	__	60
Eudragit L100	__	__	__	__	__	__	__
Eudragit EPO	__	__	42.98	__	__	42.98	42.98
Isopropyl alcohol	__	__	Q.S.	Q.S.	__	Q.S.	Q.S.
Acetone	__	__	Q.S.	Q.S.	__	Q.S.	Q.S.
Stearic acid	40	__	__	__	__	__	__
Starch 1500	40	__	__	__	__	__	__
Crosspovidone XL	60	__	__	__	__	__	__

Ingredients	F8	F9	F10	F11	F12	F13
API	42.98	42.98	42.98	42.98	42.98	42.98
Poly Ethylene Glycol 4000	42.98	42.98	42.98	42.98	42.98	__
Ethyl cellulose 4cps	25	__	__	40	__	42.98
Purified water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	__
Ethyl cellulose	__	__	__	__	__	__
Isopropyl alcohol	__	__	__	Q.S.	__	Q.S.
Methylene chloride	__	__	__	__	__	__
MCC (Avicel pH101)	230	230	230	230	230	200
Aspartame	10	10	10	10	10	10
Mannozem. EZ (spray dried mannitol)	60	60	60	60	60	__
Eudragit L100	__	21.49	14.32	__	21.49	21.49
Eudragit EPO		21.49	28.64	40	21.49	21.49
Isopropyl alcohol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Acetone	__	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Stearic acid	__	__	__	__	__	__
Starch 1500	__	__	__	__	__	__
Crosspovidone XL	__	__	__	__	__	__

MATERIALS AND METHODS

Prednisolone sodium phosphate was obtained as a gift sample from IPCA Laboratories Pvt. Ltd. Mumbai. Avicel PH101 (R.C.Rowe et al, 2003), Poly ethylene Glycol 4000 (Khankari et al, 2000, James klanck, 2001), Ethyl cellulose 4CPS, and Crospovidone XL-10 were gift sample from Signet Chemical Corporation, Mumbai. Croscarmellose sodium, Mannitol spray dried Eudragit EPO (Sheetal malke et al.2007, S.Jacob et al, 2007), Eudragit L100were gift samples from Sunrise Remedies, Ahmedabad, India. Ethyl cellulose, Aspartame, Sodium Bicarbonate, Citric acid Aerosil, and Mint flavors were obtained from DOW chemical company, Mumbai, India. All chemicals and reagents used were of analytical grade.

PREPARATION OF DRUG-STEARIC ACID SOLUTION

Weigh accurately the required quantity of API and dissolve in 129ml of water and required quantity of Stearic acid and dissolve in 200ml of IPA. Then mix drug solution to stearic acid solution. Soluble with continuous stirring for homogenous mixing for 20min.Weigh Mannozem EZ, Crosspovidone XL, Avicel pH101, and Starch1500. Then sift all the ingredients through 30# mesh. Take all ingredients in a bowel and then granulate with the help of drug-stearic acid solution to form a damp mass. Then granules are kept for drying until dried. Dried granules are passed through 35# mesh. Weigh Sodium bicarbonate, Citric acid, Aspartame, Mint flavor, Aerosil, Sodium stearyl fumarate are passed through 35# mesh and mix to the granules, one by one in a continue manner. Mix the blend conti-

Table 2: Formulation of Prednisolone ODT (30mg) Extra granulation (mg/tab)

Ingredients	F1	F2	F3	F4	F5	F6	F7
Mannozem. EZ (spray dried mannitol)	—	182.25	152.29	182.25	137.27	109.29	56.31
Crosspovidone XL 10	__	57	57	57	57	57	57
Sodium bicarbonate	15	16	16	16	16	16	16
Citric acid	20	12.5	12.5	12.5	12.5	12.5	12.5
Aspartame	18	10	10	10	15	15	15
Mint flavor	2	5	2	5	5	5	5
Aerosol (colloidal silicon dioxide)	6	2.85	2.85	2.85	2.85	2.85	2.85
Magnesium stearate	__	11.40	11.40	11.40	11.40	11.40	11.40
Sodium stearyl fumarate	12	__	__	__	__	__	__
Total(mg)	600	600	600	599.98	600	600	600
Ingredients	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	
Mannozem. EZ (spray dried mannitol)	69.13	*51.40*	51.40	14.29	*33.31*	123.31	
Crosspovidone XL 10	57	*57*	57	57	*75*	75	
Sodium bicarbonate	16	16	16	16	16	16	
Citric acid	12.5	12.5	12.5	12.5	12.5	12.5	
Aspartame	15	15	15	15	15	15	
Mint flavor	5	5	5	5	5	5	
Aerosol (colloidal silicon dioxide)	2.85	2.85	2.85	2.85	2.85	2.85	
Magnesium stearate	11.40	11.40	11.40	11.40	11.40	11.40	
Sodium stearyl fumarate	__	__	__	__	__	__	
Total(mg)	599.84	600	600	600	600	600	

nuously for 3min. Powder taste is bitter. The prepared tables are shown in table no1, 2, and 3.

Preformulation Studies

The following evaluation parameters studies were performed for the Prednisolone sodium Phosphate (Hiremath J. G et al, 2004).

Sieve Analysis

Pass a define mass of the sample through various sieves and calculate the percentage of retained powder and fines passed through sieves.

$$\text{Percentage of powder retained} = \frac{\text{Weight of the powder}}{\text{Total weight of the powder}} \times 100$$

Bulk density

It is the ratio between a given mass of powder and its bulk volume.

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Total weight of the powder}}$$

A given quantity of the powder is transferred to the measuring cylinder and it is tapped mechanically either manually or mechanical device till a constant volume is obtained. This volume is bulk volume (v) and it includes the true volume of the powder and void space among the powder particles.

Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and the horizontal plane. The granule mass should allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper.

$$\tan\theta = h/r \qquad \theta = \tan^{-1}(h/r)$$

Where, h= height of the pile

r= radius of the pile

Tapped density

Tapped density is defined as the ratio between weight of the sample powder taken and the tapped volume.

Tapped density (ρt) = M/V_f

Where, M = weight of sample powder taken

V_f = tapped volume

Compressibility index /Carr's index

Based on the apparent bulk density and the tapped density, the percentage compressibility index of the powder was determined by using the following formula.

$$\text{Compressibility index} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100$$

Table 3: Unitary formula

Materials	Percentage in a tablet	Function
Prednisolone sodium phosphate	7.16	Active Pharmaceutical Ingredient
Avicel PH101	33.33	Diluent
Poly ethylene Glycol 4000	7.16	Taste masking agent
Ethyl cellulose 4CPS	7.16	Taste masking agent
Ethyl cellulose	2.5	Taste masking agent
Mannozem EZ (Mannitol spray dried)	20.55	Sweetener
Eudragit EPO	3.58	Taste masking agent
Eudragit L100	3.58	Taste masking agent
Crospovidone XL-10	12.50	Disintegrant
Aspartame	4.16	Sweetener
Sodium Bicarbonate	2.66	Alkalizing agent
Citric acid	2.08	Buffering agent
Magnesium stearate	1.90	Lubricant
Aerosil	0.47	Glident
Mint flavors	0.83	Flavor

Label claim: Each tablet contains: Prednisolone sodium phosphate 42.98mg Equivalent to Prednisolone 30mg. Formulation 1: For 1000 Tablets. (Rowe.R.C et al, 2003, James Klancke, 2003).

Hausner's ratio

By calculating tapped density and bulk density, the Hausner's ratio can be calculated. The all parameters are reported in table no .4, 5.

Hausner's ratio = ρ_t / ρ_o

Where, ρt = tapped density

ρ_o = bulk density

In vitro dissolution testing (Kushik D et a, 2004, Shenoy V et al, 2003, Sumiya K, et al, 2000)

Dissolution study was conducted for all the formulation using USP type-II apparatus (Electolab, Mumbai, India.). The dissolution test was performed using 500 ml of Acetate buffer (PH 4.5) was taken as the dissolution medium at 50 rpm and $37^0C \pm 0.5^0C$. Five millilitres of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 270 nm. The dissolution profile and Comparative studies are also reported in Table no.7, 8 and Table no 1-8.

RESULTS AND DISCUSSION

The present investigation was undertaken to formulate Prednisolone into orally disintegrating tablet formulation for the treatment of severe inflammatory conditions allergies, arthritis, asthma, or skin reactions. Wet granulation techniques were used in formulating the drug into orally disintegrating tablet. All the experimental formulation batches have been subjected to various evaluations viz, average weight, friability, disintegration, thickness, hardness, dissolution, content uniformity and taste. Formulation F-1 was made by wet granulation using Drug-stearic acid solution and the lubricated blend taste has not met the specifications of ODT. Formulation F-2 was made by wet granulation using Ethylcellulose (1.66%) in Isopropyl alcohol as a taste masking agent and the lubricated blend taste has not met the specifications of ODT. Formulation F-3 was made by wet granulation using Eudragit EPO

Table 4: Evaluation of tablets

Formulation	Avg. Weights(mg)	Thickness (mm)	Hardness kg/cm^2)	Friability (%)	Disintegration Time (sec)
F-3	602.6	4.72	4.14	1.43	22
F-4	602.5	4.72	3.40	1.40	24
F-5	606.3	4.75	3.90	1.13	40
F-6	604.1	4.90	3.58	1.00	28
F-7	604.2	4.88	3.86	1.43	56
F-8	604.7	3.90	3.98	1.54	45
F-9	600.3	5.13	3.02	2.08	259
F-10	601.6	5.13	2.69	1.89	218
F-11	600	5.11	3.10	2.30	305
F-12	600.1	5.14	3.11	1.87	260
F-13	601.9	4.70	4.05	0.72	26

Table 5: Particle size analyses

S.No.	ASTM	Weight of mesh(A)	Weight of mesh Powder (B)	B-A	%Retained
1	100	331.9	349.2	17.3	57.66
2	140	325.8	332.2	6.4	21.33
3	200	324.1	326.4	2.3	7.66
4	Collector	539.9	543.9	4.0	13.33
Total				30.0	99.98

***Note:** Powder taken = 30 gms

Table 6: Drug solubility study (pH 1-7)

S.No.	Medium	Percentage	Mg/ml
1	D.M.Water	100.9%	0.37
2	0.1N HCl	101.5%	0.37
3	4.5 Acetate buffer	100.1%	0.36
4	6.8 Phosphate buffer	100.1%	0.36

Table 7: Dissolution profile of Orapred ODT (30mg)

Time (min)	%Drug release in Water	Time (min)	%Drug release in 0.1N HCl	% Drug release in pH 4.5 Acetate buffer
0	0	0	0	0
5	36.7	5	47.6	80.9
10	49.9	15	89.2	97.6
20	68.5	30	94.4	99.6
30	71.1	45	95.6	98.6
45	81.1	60	96.3	99.2
Assay	*88.9*		*98.6*	*99.4*

(7.16%) in Isopropyl alcohol and acetone (1:1) as a taste masking agent and the lubricated blend has good taste. In this formulation hardness and disintegration gave satisfactory results. Formulation F-4 was made by wet granulation using Ethylcellulose (2.0%) in Isopropyl alcohol as a taste masking agent and the lubricated blend after taste is bitter. In this formulation hardness and disintegration gave satisfactory results.

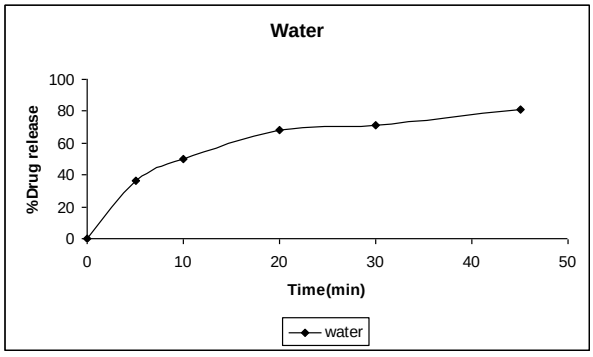

Figure 1: Dissolution profile of ORAPRED ODT in Water

Formulation F-5 was made by wet granulation using PEG4000 (6.66%) in Isopropyl alcohol and Methylene chloride as a taste masking agent, drug has to be dissolve in water and granulate with mcc and again granulate it with PEG4000 solution. And the dried granules are again granulating with Ethylcellulose (2.5%) {in Isopropyl alcohol} solution and extra granulation was carried out and the lubricated blend after taste is bitter. In this formulation hardness and disintegration gave satisfactory results. Formulation F-6 was made by wet granulation using PEG4000 (6.66%) in Isopropyl alcohol and Methylene chloride as a taste masking agent, API has to be dissolve in water and granulate with mcc and again granulate it with PEG4000 solution. And the dried granules are again granulating with Eudragit EPO (7.16%) {In Isopropyl alcohol and acetone (1:1)} solution and extra granulation was carried out and the lubricated blend after taste is bitter. In this formulation hardness and disintegration gave satisfactory results. Formulation F-7 was made by using PEG4000 in required quantity of water and API was added to PEG4000 solution granulation was done with spray-dried mcc, mannitol i.e., mannogem EZ and Aspartame. And granulate with Eudragit EPO (7.16%) in Isopropyl alcohol and acetone (1:1) solution and extra granulation was carried out and the lubricated blend after taste is bitter. In this formulation hardness and disintegration gave satisfactory results. Formulation F-8 was made by replacing Eudragit EPO solution here Ethylcellulose 4cps (4.16%) (in Isopropyl alcohol) solution and the remaining ingredients are same as formulation F-7. And the lubricated blend after taste is bitter. In this formulation hardness and disintegration gave satisfactory results. Formulation F-9, 10 &11 was made by using PEG4000 in water, API was added to it and get a clear solution granulation was done with mcc, mannitol i.e., mannogem EZ and Aspartame. For F-9 granulate

the above granules with Eudragit L100 and Eudragit EPO(1:1)(3.58:3.58) {in Isopropyl alcohol and acetone (1:1)} solution and extra granulation was carried out and the lubricated blend has good taste. In this formulation hardness and disintegration gave satisfactory results.

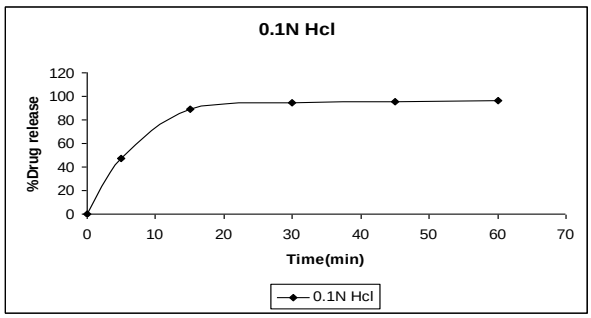

Figure 2: Dissolution profile of ORAPRED ODT in 0.1N Hcl

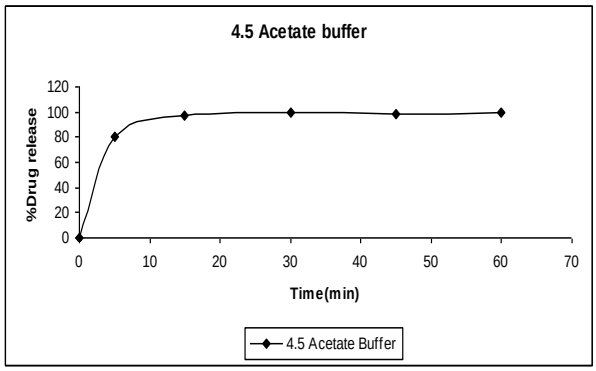

Figure 3: Dissolution profile of ORAPRED ODT in 4.5 Acetate buffer

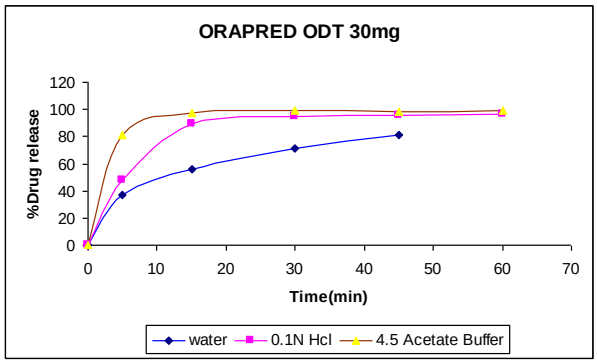

Figure 4: Dissolution profile of ORAPRED ODT in different media

Formulation F-10 granulate the above granules with Eudragit L100 and Eudragit EPO(1:2)(4.77:2.38) {in Isopropyl alcohol and acetone (1:1)} solution and extra granulation was carried out and the lubricated blend has good taste. In this formulation hardness and disintegration gave satisfactory results. Formulation F-11 granulate the above granules with Ethylcellulose 4cps(6.66) in IPA and dried granules are again granulate with Eudragit EPO(6.66) {in Isopropyl alcohol and acetone (1:1)} solution and extra granulation was carried out and the lubricated blend has good taste. In this formulation hardness and disintegration gave satisfactory results. Formulation F-12 was reproducibility of F-9 Batch with change in percentages of Mannozem EZ (5.55%) and crospovidone XL10 (12.5%) and lubricated blend has good taste. In this formulation hardness and disintegration gave satisfactory results. Formulation F-13 was made by Ethylcellulose4cps and API are mixed and granulate with Isopropyl alcohol and mix the remaining intra granular ingredients and granulate with Eudragit L100 and Eudragit EPO(1:1){in Isopropyl alcohol and acetone (1:1)} solution and extra granulation was carried out and the lubricated blend has good taste.

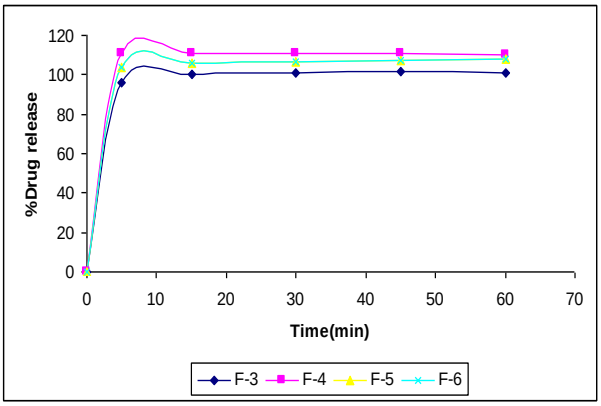

Figure 5: Dissolution profile of Formulations F-3, F-4, F-5, and F-6

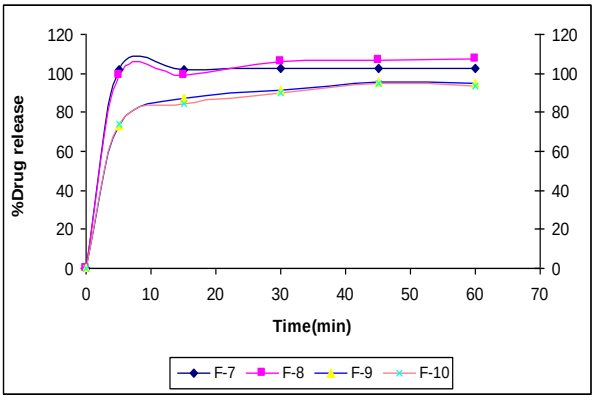

Figure 6: Dissolution profile of Formulations F-7, F-8, F-9, and F-10

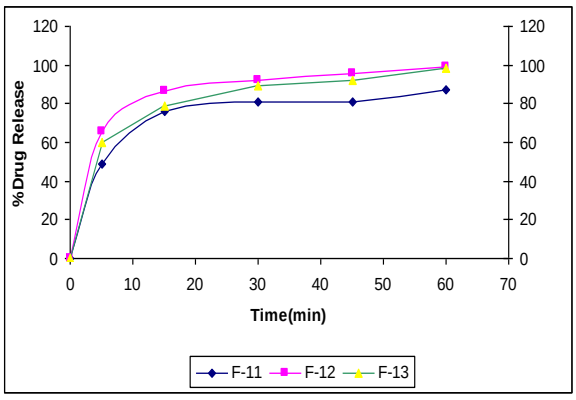

Figure 7: Dissolution profile of Formulations F-11, F-12, and F-13

Table 8: Cumulative Percentage of Drug Release in pH 4.5 Phosphate Buffer

Sampling Time in min	Cumulative Percentage of Drug Release in *pH 4.5 Phosphate Buffer*.										
	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12	F-13
5	96.3	110.6	103.5	103.5	101.8	99.1	73.2	74.2	48.5	65.3	60.3
15	100.1	111.0	105.9	105.9	102.2	99.2	87.4	84.6	76.1	86.7	78.7
30	100.8	110.8	106.6	106.6	102.4	106.1	91.7	89.8	80.6	92.2	89.1
45	101.3	110.6	107.3	107.3	102.4	106.5	95.8	95.2	80.6	95.7	92.4
60	101.2	110.0	107.8	107.8	102.4	107.4	95.0	93.3	87.5	99.4	98.1
Assay	*100.7*	*109.7*	*106.2*	*101.9*	*100.6*	*104.9*	*89.0*	*88.8*	*80.1*	*99.7*	*99.2*

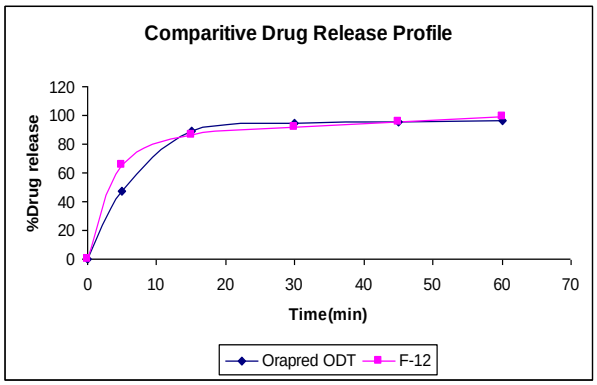

Figure 8: Dissolution profile of ORPRED and Formulation F-12

SUMMARY AND CONCLUSION

The demand for orally disintegrating tablets has enormously increased during the last decade. Particularly for geriatric and pediatric patients who have difficulty in swallowing conventional tablets and capsules. Oral administration of the drugs is difficult in patients having concomitant vomiting or diarrhea. Fast dissolving or fast disintegrating dosage form is advantageous for such patients. Fast dissolvable or fast disintegrating dosage forms are meant to disintegrate immediately upon contact with the saliva leading to faster release of drug in the oral cavity. Because administrating the fast disintegrating dosage forms, absorption of the drugs occurs through buccal mucosa and it may reduce In present work wet granulation technique was employed to prepare tablets. Microcrystalline cellulose is used as diluent. Aspartame and mannitol is used as sweetening agents. Crospovidone XL10 as disintegrant. Prednisolone Sodium Phosphate was having bitter taste and to mask the bitter taste flavoring agent like mint flavour and taste masking agents like PEG4000, Ethylcellulose 4cps, Eudrait EPO and Eudragit L100. Post compressional parameters hardness, friability, weight variation, disintegration time, drug content and dissolution studies are studied. Taste, disintegration and dissolution profile of best formulations F-12 and F-13 are better than marketed product i.e. ORAPRED.

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