Available Online through
www.ijpbs.com

IJPBS |Volume 2| Issue 2 |APRIL-JUNE |2012|30-41

Formulation, Characterization and *in vitro* evaluation of Orodisipersible taste masking tablets of prednisolone sodium phosphate

Arun D, Venu gopal N, Shekar L, Ramarav B, J.V.RAO, KARUNAKAR K, SURENDRA Y*

Department of Pharmaceutics

Tallapadmavathi College of Pharmacy, Orus-506002, Warangal, Andhra Pradesh, India.

***Corresponding Author Email: arundelight@gmail.com**

PHARMACEUTICAL SCIENCES

RESEARCH ARTICLE

RECEIVED ON 03-02-2012

ACCEPTED ON 25-04-2012

ABSTRACT

In present research work an attempt was made to develop and evaluate orodipersible taste masked prednisolone sodium phosphate by direct compression method and by using cross povidone, cross carmellose sodium and sodium starch glycolate as superdisintegrants. Predinisolone sodium phosphate was having bitter taste and to mask the bitter taste, taste masking agents like ethyl cellulose, eudrait EPO and eudragit L100 were used. In the preformulation studies it has been proved that there is no interaction between the drug and the excipients. The blends of varying super disintegrants and the taste masking agents were formulated into nine formulations and the blends were evaluated for the pre and post comparison parameters and In vitro drug release is also studied. All the pre compression parameters are within the limits. The results shown that the formulations containing the Cross povidone have the good flow properties and the good compactability when compared with the other formulations. The results shown maximum for the formulation (ODT_1) that containing the cross povidone as superdisintegrant and Eudragit EPO as taste masking agent. The In vitro drug release of formulation ODT_1 had shown that maximum drug release 99.4 ± 0.54 when compared with the other formulations. So ODT_1 was choosen as the best formulation which contains crosspovidone as a super disintegrant and Eudragit EPO as a taste masking agent.

KEYWORDS: *prednisolone sodium phosphate, Orodisipersible Tablets, taste masking, in vitro drug release.*

INTRODUCTION

ODTs offer all advantages of solid dosage forms along with special advantages, include: They provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.

Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.Medication as *bitter pill* has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs.Bioavailability of drugs that are absorbed from mouth, pharynx, and esophagus is increased.Pre-gastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increases the bio-availability.

Advantages of ODT's

- For acute conditions, this dosage form is easier for patients to take anytime, anywhere those symptoms occur.
- For chronic conditions, it is assumed to improve compliance.
- Ease of swallowing for patients and convenience of taking the medication anytime without the need of water.

ODT development consists of three parts: Evaluating the need to taste mask the drug. Incorporating the taste masked/non-taste masked

- Drug into the tablet matrix.
- Packaging.

CHALLENGES TO DEVELOP ODT[1]

1. Rapid disintegration of tablet
2. Have sufficient mechanical strength
3. Minimum or no residue in mouth
4. Protection from moisture
5. Good package design
6. Swallowability
7. Bio-availability and Stability

PROCESSES EMPLOYED IN FORMULATING ODTs[2]

1. Lyophilization of Freeze-drying
2. Molding
3. Cotton Candy process
4. Spray Drying
5. Mass extrusion and
6. Compaction

Selection of ODT drug candidates[3]

- In general, an ODT is formulated as a bioequivalent line extension of an existing oral dosage form. Under these circumstances, it is assumed that the absorption of a drug molecule from the ODT occurs in the post-gastric GIT segments, similar to the conventional oral dosage form.
- It is possible that these differences may, in part, be attributed to the drug molecule, formulation, or a combination of both. If significantly higher plasma levels and systemic exposure have been observed, pre-gastric absorption leading to the avoidance of first-pass metabolism may play an important role.
- This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT. For example, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT.

TASTE-MASKING AGENTS PRINCIPLE[4]

Taste masking of drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer systems or complexation. The approaches are as follows:

- Layering the drug onto inert beads using a binder followed by coating with a taste-masking polymer.
- Granulating the drug and coating with a taste masking polymer.
- Spray drying the drug dispersed or dissolved in a polymeric solution to get taste-masked particles.
- Complexation by the use of inclusion in cyclodextrins.
- Psychological modulation of bitterness.

- Coacervation to form microencapsulated drug within a polymer.
- Formation of pellets by extrusion spheronization.

MATERIALS AND METHODS

Prednisolone sodium phosphate was received as a gift from IPCA Laboratories. Eudragit EPO, Eudragit L100, Aerosil were obtained from M/s. DEGUSSA, Avicel PH101 was received from FMC Polymers, Mannitol spray dried (SPI polyol, 321, new castle), Crospovidone XL-10, Cross carmellose sodium were purchased from M/s. ISP Technologies. Aspartame (Neutrasweet pharma agencies), Sodium starch glycollate (Merck chemicals), Mint flavors (Pan aroma, Chennai).

PREFORMULATION STUDIES[5]:

Identity parameters of blend:

The identity evaluation parameters studies like solubility, molecular conformation by IR, percentage of various impurities and drug content for pure drug by assay were performed for the Prednisolone sodium Phosphate.

1. Sieve Analysis:

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

2. Solubility study:

Excess of drug was added to 20ml of phosphate buffer still saturation was established, during successive addition of drug in buffer 2ml of sample withdrawn and analysed spectrophotometrically at 254 nm until constant absorbance was observed.

3. Bulk density: It is the ratio between a given mass of powder and its bulk volume.

4. 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.

5. Tapped density:

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

6. 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.

7. Hausner ratio:

By calculating tapped density and bulk density, the Hausner ratio can be calculated.

8. Loss on drying (% LOD)[7]

Loss on drying is an expression of moisture content, which is calculated as follows: Tare a glass stoppered, shallow weighing bottle that

has been dried for 30 minutes in the drying chamber. Put the test specimen in the bottle, replace the cover and accurately weigh the bottle and the contents. By gently, sidewise shaking, distribute the test specimen as evenly as practicable to adepth of about 5mm. place the loaded bottle with the removed stopper in the drying chamber. After a time of 3 hrs at 105º C the test specimen is removed, allowed to cool and then reweighed. The % LOD must not be more than 2% W/W.

Percentage of LOD is calculated using the formula

% LOD = Wt. of water in sample / Total Wt. of wet sample x 100

DRUG – EXCIPIENT COMPATIBILITY STUDIES

Fourier transforms infra red spectroscopy (FTIR)

The FTIR analysis was conducted for the structure characterization. FTIR spectra of the pure drug, pure polymers and mixture of both were recorded. Formulations were taken in a KBr pellet using BOMEN MB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade Kbr; samples were scanned in the IR range from 500 to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

Each tablet contains Prednisolone sodium phosphate equivalent to Prednisolone 30 mg.

FORMULATION OF PREDNISOLONE SODIUM PHOSPHATE ORODISPERSIBLE TABLETS:

Nine formulations (ODT_1, ODT_2, ODT_3, ODT_4, ODT_5, ODT_6, ODT_7, ODT_8, and ODT_9) are varying superdisintegrants and tastemasking agents are formulated.Crospovidone, Cross carmellose sodium and Sodium starch glycolate are choosed as superdisintegrants and Eudragit EPO, Eudragit L100 and ethyl cellulose are choosed as tastemasking agents. Direct compression method is choosed for formulation

Formulation of predinisolone sodium phosphate tastemasked orodipersable tablets

Prednisolone tablets were formulated by using direct compression method. All the ingredients were weighed and then directly compressed to form tablet.

Table-1 FORMULATION OF PREDNISOLONE ODT (30mg)

INGREDIENTS	QUANTITY OF INGREDIENTS IN mg								
	ODT_1	ODT_2	ODT_3	ODT_4	ODT_5	ODT_6	ODT_7	ODT_8	ODT_9
API	42.98	42.98	42.98	42.98	42.98	42.98	42.98	42.98	42.98
Crospovidone XL-10	8	8	8	-	-	-	-	-	-
Crosscarmellose sodium	-	-	-	8	8	8	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	10	10	10
Eudragit EPO	16	-	-	16	-	-	16	-	-
Eudragit L100	-	16	-	-	16	-	-	16	-
Ethyl cellulose	-	-	10	-	-	10	-	-	10
Avicel PH 101	24	24	30	24	24	30	22	22	28
Aspartame	20	20	20	20	20	20	20	20	20
Mannitol	50	50	50	50	50	50	50	50	50
Aerosil	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Mint flavour	5	5	5	5	5	5	5	5	5

EVALUATION OF PREDINISOLONE ORODISPERSIBLE TABLETS

Pre compression parameters[6]

The Angle of repose, Bulk density, Tapped density, Compressibility Index, Hausner ratio and % LOD was calculated.

Post compression parameters

Thickness, Hardness test, Weight variation test, Friability test, Disintegration, Water absorption Ratio, Content uniformity test, Wetting time, In-vitro dispersion time were calculated.

In vitro dissolution studies

Preparation of pH 6.8 phosphate buffer

50 ml of monobasic potassium phosphate solution was placed in a 200 ml volumetric flask, to it 22.4 ml of 0.2 M sodium hydroxide was added and the volume was then made up to 200 ml with distilled water.

Standard curve of Prednisolone sodium phosphate in phosphate buffer pH 6.8

100mg of Prednisolone sodium phosphate was dissolved in phosphate buffer pH 6.8 in a 100ml standard flask and filled up to the mark using phosphate buffer pH 6.8. Serial dilutions were made in phosphate buffer pH 6.8 in order to obtain 5 µg/ml, 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml. Absorbance of these solutions were measured at 254 nm using UV-Visible Spectrophotometer [Schimadzu 159] and standard graph was plotted.

Procedure:

Tablet dissolution was assessed using standard USP dissolution apparatus type II. The dissolution media used was 900ml of 6.8 phosphate buffer .The temperature was

maintained at 37 ± 0.5ºC. At predetermined time intervals, an aliquot of 5 ml sample was withdrawn, and made up to 10 ml with suitable diluent.

Dissolution parameters:

Apparatus	:	USP2, Paddle.
Medium	:	6.8 phosphate buffer.
Medium volume	:	500 ml.
Medium Temp	:	37 ±0.5 °C.
Paddle speed	:	50 rpm.
Sampling Time	:	60 min
Sampling Time Points (profile)	:	5, 10, 20, 30, 45, 60 min.
Sampling volume	:	5 ml

Chromatographic conditions for Dissolution and Assay:

Column	:	Kromosil C18, (150×4.6mm), 5µm.
Flow rate	:	1.0ml/min
Wave length	:	UV-254
Column Temperature	:	30°C
Injection volume	:	20µl
Run time	:	15min.

RESULTS AND DISCUSSION

Preformulation studies

Identity Parameters of API.

Table 2: Identity Parameters of API

S.No	Test	Specifications	Results
1.	Description	Off-white to beige colored powder.	Complies
2.	Solubility	Soluble in water, slightly soluble in chloroform.	Complies
3.	Identification: IR-Spectrum	IR-Spectrum of the test sample should match with the IR-Spectrum of the working standard.	Complies
4..	Related substances (by HPLC) Impurity-A* Impurity-B* Any other impurity Total Impurities	 Not detected Not detected 0.09% 0.19%	 NMT 0.15 NMT 0.15 NMT 0.10 NMT 1.00
5.	Assay	99.9% w/w	NLT 98.0% w/w & NGT 102.0% w/w. calculated on dried substance.

- **All the Identity parameters of the API are found to be within the limits.**

PARTICLE SIZE ANALYSIS

Table 3: Particle size analysis

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.

$$\%\text{Retained} = \frac{\text{B-A}}{\text{Weight of powder taken}} \times 100$$

The particle size analy of the pure drug shown that the highest % retained is found at the sieve size having the 100 µm and then the % retained is found at the sieve have the size range 140 µm

Solubility study:

Solubility study was carried out in pH 6.8 phosphate buffer. Excess of drug added to20ml of phosphate buffer still saturation was established, during successive addition of drug in buffer 2ml of sample withdrawn and analysed spectrophotometrically at 254 nm until constant absorbance was observed. Solubility was found to be 0.36 mg/ml.

Physical parameters

Table 4: Physical parameters in preformulation studies

S.No	parameters	Result
1.	Tapped density	0.728 gm/ml
2.	Bulk density	0.521 gm/ml
3.	Compressibility Index	28.40 %
4.	Hausner Ratio	1.397
5.	Angle of repose	29.30º

The pure drug shown that angle of repose value is 29.30º indicates the flow of the drug is good. The compressibility index, Hausners ratio values of the drug are 28.40 and 1.397 indicates that the drug has poor compressibility properties.

Drug Excipient compatible studies:

Fig- 1 FTIR of prednisolone Sodium phosphate

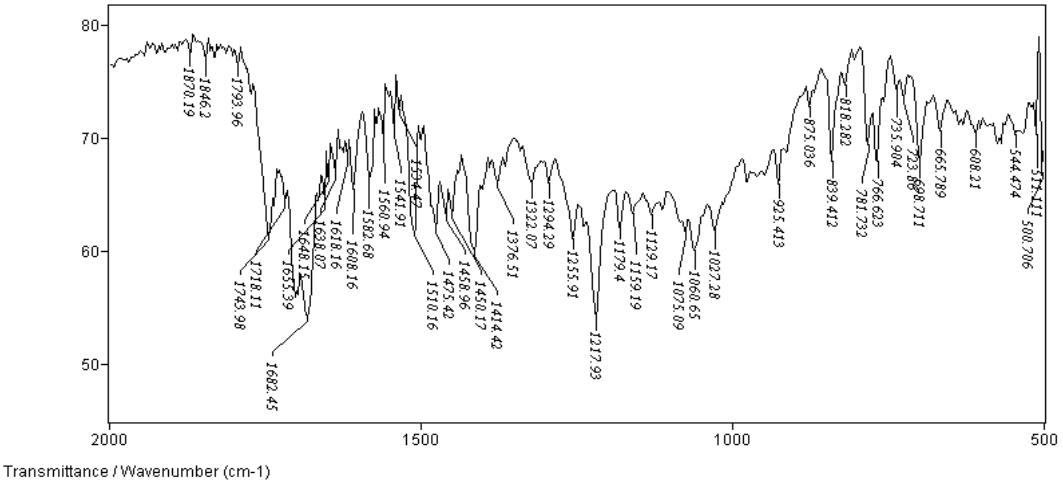


Fig- 2 FTIR of Placebo

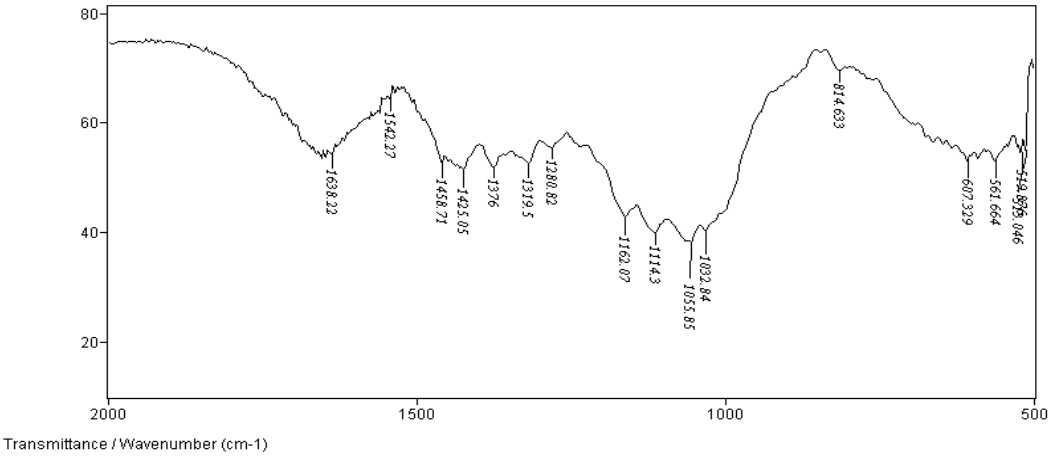
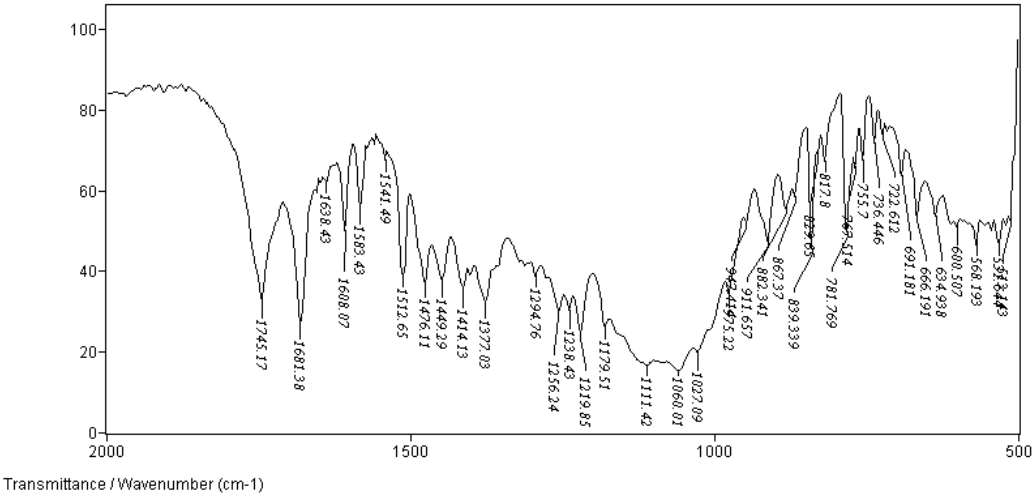


Fig- 3 FTIR of ODT_1 Formulation



The FTIR of Presinisolone (drug) show intense band at 1613.36 cm^{-1}, 1566.76 cm^{-1} , 1515.59 cm^{-1} and 1052.22 cm^{-1} corresponding to the functional groups C=O, COOH, NH and OH bending as shown in **Figure 1** . The FTIR of best formulation ODT_1 shown intense bands at 1617.75 cm^{-1},1560.85 cm^{-1} , 1517.38 cm^{-1} and 1052.19 cm^{-1} indicates no change in the functional groups C=O, COOH, NH and OH as shown in **Figure 2**. The FTIR of Placebo shown that there are no intense bands at groups C=O, COOH, NH and OH this shows that drug peaks are missing in it as shown in **Figure 3**. From the above interpretation it is understood that there is no major shifting in the frequencies of above said functional groups. Hence these drug and polymers are compatible with each other.

EVALUATION OF PREDINISOLONE ORODISPERSIBLE TABLETS

Table 05-Precompression properties

Formulation	Angle of repose (^{0})	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index
ODT_1	27.46 ± 0.5	0.65 ± 0.02	0.74 ± 0.01	13.88 ± 0.6
ODT_2	25.25 ± 0.6	0.63 ± 0.01	0.74 ± 0.03	15.14 ± 0.6
ODT_3	28.45 ± 0.47	0.64 ± 0.01	0.73 ± 0.03	15.31 ± 0.08
ODT_4	27.01 ± 0.7	0.66 ± 0.03	0.73 ± 0.03	14.46 ± 0.4
ODT_5	25.25 ± 0.6	0.63 ± 0.01	0.75 ± 0.04	14.34 ± 0.02
ODT_6	26.10 ± 0.5	0.64 ± 0.01	0.73 ± 0.03	14.60 ± 0.24
ODT_7	26.98 ± 0.24	0.64 ± 0.01	0.71 ± 0.05	14.57 ± 0.54
ODT_8	27.21 ± 0.41	0.64 ± 0.01	0.72 ± 0.01	14.48 ± 0.21
ODT_9	25.12 ± 0.6	0.66 ± 0.02	0.74 ± 0.03	15.56 ± 0.36

Table 06: Precompression properties

Formulation	Hausner's Ratio	% LOD
ODT_1	1.37 ± 0.16	0.82 ± 0.36
ODT_2	1.29 ± 0.05	1.06 ± 0.41
ODT_3	1.32 ± 0.02	0.96 ± 0.58
ODT_4	1.32 ± 0.02	0.62 ± 0.02
ODT_5	1.36 ± 0.07	0.88 ± 0.37
ODT_6	1.29 ± 0.05	1.15 ± 0.51
ODT_7	1.19 ± 0.07	1.1 ± 0.40
ODT_8	1.43 ± 0.21	1.03 ± 0.34
ODT_9	1.25 ± 0.05	1.08 ± 0.40

Table 07: Postcompression properties

Formulation	Weight variation (mg)	Thicknes(mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (sec)
ODT_1	180.0 ± 0.12	4.72 ± 0.14	3.40 ± 0.14	0.74 ± 0.15	24 ± 0.01
ODT_2	179.8 ±1.12	4.90 ±0.74	3.90 ± 0.14	0.65 ± 0.07	28 ± 0.02
ODT_3	180.2 ± 0.54	4.88 ± 0.21	3.58 ±0.23	0.93 ±0.05	27 ± 0.14
ODT_4	180.3 ± 0.63	4.96 ± 0.14	3.86 ± 0.47	0.97 ± 0.02	26 ± 0.25
ODT_5	179.9 ± 0.87	4.87 ± 0.32	3.98 ± 0.21	0.83 ± 0.06	27 ± 0.14
ODT_6	180.5 ± 0.36	4.96 ± 0.47	3.62 ± 0.36	0.80 ± 0.12	25 ± 0.14
ODT_7	180.2 ± 0.74	4.63 ± 0.54	3.12 ± 0.41	0.79 ± 0.10	26 ± 0.36
ODT_8	180.4 ± 0.52	4.78 ± 0.47	3.10 ± 0.74	0.75 ± 0.15	24 ± 0.14
ODT_9	179.6 ± 0.14	4.66 ± 0.47	3.11 ± 0.74	0.81 ± 0.10	29 ± 0.14

Table 08: Postcompression properties

Formulation	Water absorption Ratio	Assay	Wetting time (sec)	In-vitro dispersion time(Sec)
ODT_1	78.92 ± 0.14	99.19 ± 0.51	21 ± 0.24	28 ± 0.14
ODT_2	72.35 ± 0.41	98.42 ± 1.01	24 ± 0.14	29 ± 0.14
ODT_3	69.32 ± 0.58	97.77 ± 1.26	28 ± 0.17	32 ± 0.25
ODT_4	75.63 ± 0.47	97.53 ± 1.82	25 ± 0.12	31 ± 0.63
ODT_5	74.21 ± 0.25	99.82 ± 0.33	32 ± 0.32	34 ± 0.24
ODT_6	74.23 ± 0.14	100.55 ± 0.58	33 ± 0.54	32 ± 0.21
ODT_7	76.32 ± 0.25	100.25 ± 2.94	28 ± 0.36	29 ± 0.41
ODT_8	77.12 ± 0.54	99.40 ± 0.94	29 ± 0.65	33 ± 0. 63
ODT_9	74.12 ± 0.14	101.63 ±1.50	31 ± 0.14	32 ± 0.45

INVITRO DRUG RELEASE

Standard plot of prednisolone sodium phosphate in 6.8 pH phosphate buffer:

Table 09: Standard plot of prednisolone sodium phosphate

S.No	Concentration(µg/ml)	Absorbance at 254 nm
1	10	0.234
2	20	0.365
3	30	0.564
4	40	0.678
5	50	0.987

Fig- 10 Standard plot of prednisolone sodium phosphate

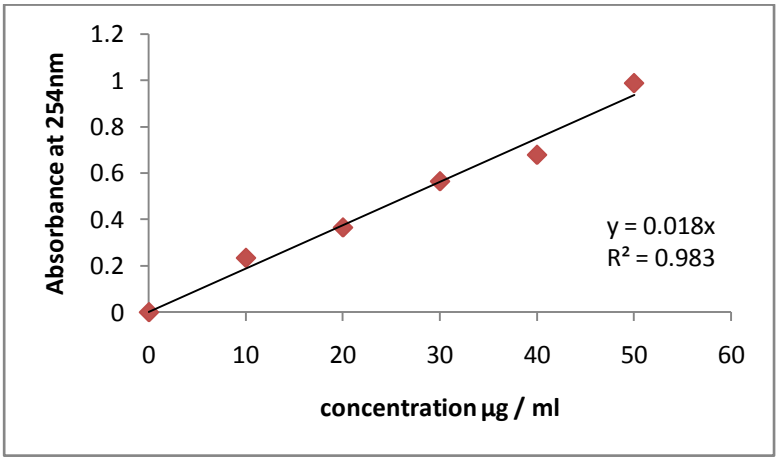


Table 11: Cumulative Percentage drug Release of ODT_1 – ODT_3 in pH 6.8 Phosphate Buffer.

Sampling Time in min	Cumulative Percentage Of Drug Release in *pH 6.8 Phosphate Buffer*.		
	ODT_1	ODT_2	ODT_3
5	74.2 ± 0.12	65.4 ± 0.45	60.3 ± 0.54
10	80.3 ±0.21	78.6 ± 0.36	71.2 ± 1.25
20	86.7 ± 0.36	84.6 ± 0.14	78.7 ± .78
30	92.2 ± 0.14	89.8 ± 0.74	85.1 ± 0.97
45	95.7 ± 0.47	93.3 ± 0.14	90.5 ± 0.96
60	99.4 ± 0.54	95.2 ± 0.54	93.6 ± 0.74

DISCUSSION

The *In vitro* drug release of tablets containing the crosspovidone as superdisintegrant shown the the minimum drug release that is 93.6 ± 0.74 for ODT_3 and maximum drug release at 99.4 ± 0.54 for ODT_1.

The *In vitro* drug release of tablets containing the crosscarmellose sodium as super disintegrant shown the the minimum drug release that is 91.1 ± 0.14 for ODT_6 and maximum drug release at 97.5 ± 0.74 for ODT_4.

The *In vitro* drug release of tablets containing the sodium starch glycolate as superdisintegrant shown the minimum drug release that is 89.1 ± 0.54 for ODT_7 and maximum drug release at 90.12 ± 0.87for ODT_9.The maximum drug release that is 99.4 ± 0.54 shown for the crosspovidone containing superdisintegrant ODT_1 Containing Eudragit EPO as taste masking agent at the end of 1 hr.

REFERENCES

1. HowardC.AnselLloyd;V.Allen;Jr.Nicolas;G.Popovich Pharmaceutical Dosage forms and Delivery systems;pg.no.209.
2. US Food and Drug Administration, CDER Data Standards Manual, 2003, http://www.fda.gov/cder/dsm/DRG/drg00201.htm accessed March 19, 2005.
3. S.R. Cherukruri and R. Fuisz, "Process and Apparatus for Making Tablets and Tablets Made Therefrom," European Patent 0,677,147 A2 (1995).
4. D. Brown, "Orally Disintegrating Tablets: Taste Over Speed," Drug Deliv. Technol. 3 (6), 58–61 (2001)
5. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, eds. *Tutorial Pharmacy*. New Delhi, India: CBS Publishers and Distributors; 1986:211-233.
6. Indian Pharmacoepoia.; vol II; Controller of publications, Ministry of Health. 1996. 789- 801.
7. Encyclopedia of pharmaceutical technology; 3rd edition; James swarbrick; Vol.6; 2614-2629.

***Corresponding Author:**
ARUN DULAM*
Tallapadmavathi College of Pharmacy, Orus-506002, Warangal, Andhra Pradesh, India.