FORMULATION AND EVALUATION OF PERINDOPRIL ORAL DISINTEGRATING TABLETS

Jyothirmai Channamsetty [1]*, Dr.V. Anitha Kumari [1], Dr.N.B.V Siva Ram[1], Ramya Sri.S[2]

[1]Department of Pharmaceutics, Nova College of Pharmacy ,Vegavaram ,West Godavari, Andhra Pradesh , India.

[2]Department of Pharmaceutics, University College of Technology,Osmania University, Hyderabad, Telangana, India

Corresponding Author:

Jyothirmai Channamsetty,
Department of Pharmaceutics,
Nova College of Pharmacy,
Vegavaram (V), West Godavari(Dist.),
Andhra Pradesh , India.

ABSTRACT

Difficulty in swallowing is common among all age groups especially elderly and pediatrics. Oral disintegrating tablets may constitute and innovative dosage form that overcome the problem of swallowing and provide a quick onset of action. This study was aimed to formulate and evaluate an orally disintegrate tablet (ODT) containing Perindopril while using Superdisintegrants. Oral disintegrate tablets were prepared by direct compression by using Superdisintegrants CroscarmelloseSodium,Crospovidone and Sodium starchglycolate. The prepared tablets were evaluated for hardness, friability, thickness, drug content uniformity. According to the results of optimized batches the concentration of superdisintegrant were given rapid disintegration in 24 seconds which showed 99.78 % drug release within 45 minutes. Crospovidone superdisintegrant, gives a rapid disintegration and when used in formulation of ODT.

Key Words: Perindopril, CroscarmelloseSodium,Crospovidone, Sodium starchglycolateand Oral Disintegrating Tablets.

INTRODUCTION:

Most of the pharmaceutical dosage forms are formulated for oral administration where, direct ingestion is intended. In such cases like those with conventional dosage forms, chewing

imposes issue in pediatric and the geriatric patients form in. Further psychiatric patients, hospitalized or bedridden patients with chronic diseases finds difficult to swallow solid oral dosage. It is expected that Orally disintegrating tablets (ODTs) can address such critical issues. ODTs are solid dosage form that provides the rapid disintegration or dissolution of solid to present as solution or suspension form even when placed in the mouth under limited bio-fluid. These Orally disintegrating tablets have various synonyms such as or dispersible tablets, quick disintegrating tablets, and mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. The excipients which are used in ODT technology are usually hydrophilic in nature that could be selected on the basis of drug's physicochemical properties, especially, hydrophillicity or hydrophobicity. If the drug is hydrophobic then dosage form is termed disintegrating tablets whereas, if the drug is hydrophilic then it is called fast dissolving tablets [2-3].

Ideal Characteristics Of ODTS :

ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include

1. It should dissolve or disintegrate in the mouth usually within fraction of seconds. There is no requirement of water for swallowing purpose.

2. It should provide pleasant feeling in the mouth.

3. It should be compatible with taste masking agents.

4. It should be portable without fragility concern.

5. ODTs leave negligible or no residue in the mouth after oral administration.

6. ODTs exhibit low sensitivity to altered environmental conditions such as humidity and temperature.

7. ODTs allow high drug loading.

8. Adaptable and amenable to conventional processing and packaging equipment at nominal expense.

ADVANTAGES OF ODTs

1. ODT can be administer to the patients who cannot swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, patients with esophageal problems & patients who

refuse to swallow such as pediatric, geriatric & psychiatric patients and thus improves patient compliance. 2. It contain the certain studies which concluded increased bioavailability and proved rapid absorption of drugs through pregastric

3. Absorption of drugs from mouth, pharynx & esophagus as saliva passes down.

4. ODT is most convenient for disabled, bedridden patients, travelers and busy people, who do not always have access to water.

5. Good mouth feel property of ODT helps to change the perception of medication.

6. As bitter pill particularly in pediatric patients.

Requirements of fast dissolving tablets

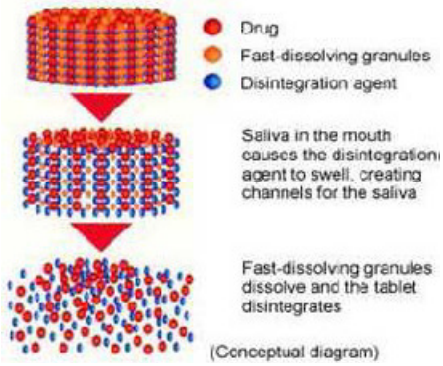

Fig : Conceptual diagram of ODTs.

Excipients used for the preparation of FDT

FDT contain one superdisintegrant, a diluent, a lubricant. Contain optionally a swelling agent, a permeabilizing agent, sweeteners and flavouring agents.

Important criteria for excipients used in formulation of ODTs [14]

1. Should disintegrate rapidly.

2. Do not interact with the drugs in formulation.

3. Should be chemically inert.

4. Should not affect the efficacy of formulation.

5. Should not alter the organoleptic characteristics of the product.

6. Should be stable.

7. Should melt in the range of 30-35°C

1st generation ODTs

Cardinal health care developed and commercialized lyophilization method as Zydis®. For thepreparation of product, drug suspensions with specific additives are freeze dried and thenfilled into the pockets of the press through packing (PTP).

2nd generation ODTs

This method was the wet mass of drugs and additives are tabletted prior to drying andcommercialized as EPM® tablets.

3rd generation ODTs

In this method dry mass of the drug and saccharides are tabletted. Researchers haveapproached various modifications in this method for preparation of different types of ODTs.For example, in WOWTAB-DRY® the tablet was prepared by application of the crystallinetransition of amorphous sucrose. Another product Ora Solv® was prepared by low pressurecompression technique using foaming agents. Flash tab® was also prepared by low pressurecompression method using dry powder granules with drug, disintegrants and microcrystallinecellulose.

MATERIALS

PerindoprilProcured From Glenmark Pvt. Ltd., Mumbai. Provided by **SURA LABS, Dilsukhnagar, Hyderabad.**CroscarmelloseSodium, Lactose from Oxford Laboratories Pvt. Ltd, Mumbai, India, Crospovidone, Sodium starchglycolate, Mannitol from S.D. Fine chemicals, Mumbai, India, and Talc, Mg.StearateRubicon Research Pvt. Ltd.,Mumbai, India provided by **SURA LABS, Dilsukhnagar, Hyderabad.**

METHODOLOGY

Analytical method development forPerindopril:

Buffer preparation:

Preparation of 0.2 M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.128 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 ml of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution : Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Preparation of pH 6.8 phosphate buffer : Accurately measured 250 mL of v0.2 M potassium dihydrogen orthophosphate and 112.5 mL of 0.2 M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400 nm against the reagent blank to fix absorption maxima. The λmax was found to be 387.2nm. Hence all further investigations were carried out at the same wavelength.

b) Construction of standard graph

100 mg of Perindopril was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL) 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 1.0 ml, 2.0ml, 3.0 ml, 4.0 ml, 5 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 10,20,30,40 and 50µg/ml respectively. The absorbance of each concentration was measured at respective (λmax) i.e., 387.2nm

Formulation development:

Drug and different concentrations of super disintegrants (Sodium starch glycolate, Cross caramellose Sodium, Cross povidone)and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass motor for 15 min.

- The obtained blend was lubricated with magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 min.

The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations

Table: Formulation table showing various compositions

INGREDIANTS	FORMULATIONS								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Perindopril	8	8	8	8	8	8	8	8	8
Croscarmellose Sodium	4	8	12	-	-	-	-	-	-
Crospovidone	-	-	-	4	8	12	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	4	8	12
Talc	5	5	5	5	5	5	5	5	5
Mg.Stearate	5	5	5	5	5	5	5	5	5
Mannitol	10	10	10	10	10	10	10	10	10
Lactose	68	64	60	68	64	60	68	64	60
Total weight	100	100	100	100	100	100	100	100	100

The tablets were prepared by using tablet compression machine . The hardness of the tablet was maintained as (2.25-2.48) kg/cm^2

Evaluation of tablets:

Pre compression parameters:

Measurement of Micromeritic properties of powders

1.Angle of repose : $\tan \Theta = h/r$ ……(1)

Where , h and r are the height and radius of the powder cone.

2. Bulk density: M/V_0 ……. (2)

V_0 = apparent unstirred volume

M= Powder mass

3. Tapped density: M/V_f …… (3)

M = weight of sample powder taken

V_f = Tapped volume

4. **Compressibility index:** Carr's Index (%) = [(TD-BD)/TD] x100 …… (4)

5. Hausner's ratio : H = Pt / ρB …….(5)

where ρT= tapped density, ρB = bulk density

H = Pt / ρB …….(5)

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Post compression parameters

a) **Thickness**

The thickness of the tablets was determined by using Digital micrometer. 10 individual tablets from each batch were used and the results averaged.

b) **Weight variation**

Twenty tablets were randomly selected from each batch and individually weighed . The average weight and standard deviation 3 batches were calculated. It passes the test for weight variation test if not more than 2 of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the % shown. It was calculated on an electronic weighing balance.

c) **Friability**

The friability values of the tablets were determined using a Roche-friabilator . Accurately weighed six tablets were placed in The Roche friabilator and rotated at 25 RPM for 4 min. Percentage friability was calculated using the following equation.

Friability = ([w_0-w]/w_0) x 100

Where w_0 = weight of tablet at time zero before revolution.

w = weight of the tablet after 100 revolutions

d) Drug content

The content of drug carried out by 5 randomly selected tablets of each formulation . The 5 tablets were grinded to get powder , this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analysed spectrophotometrically at 387.2nm using UV spectrophotometer . Each measurement was carried out in triplicate and the average drug content was calculated.

e) Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 min. and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

f) Dissolution test of Perindopril

Drug release from Perindopril tablets was determined by using dissolution test USP 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 medium as the dissolution medium of quantity 900 ml. The whole study is being carried out at room temperature of 37˚ C and at a speed of 75 RPM.

5 ml aliquots of dissolution media were withdrawn each time intervals (5, 10, 15, 20, 30, min) and appropriate dilution by UV spectrophotometer. The concentration was calculated using standard calibration curve.

Drug-Excipients compatibility studies:

Drug excipients compatibility studies were carried out by mixing the drug with various excipiennts in different proportions (in 1;1 ratio were to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly. Fourier Transform Infrared Spectroscopy (FTIR) studies were performed on drug, optimized formulation using Bruker FTIR. The samples were analyzed between wave numbers 4000 cm^{-1} and 550 cm^{-1}.

RESULTS AND DISCUSSION

Preparation of calibration curve of Perindopril:

The regression coefficient was found to be 0.999 which indicates a linearity with an equation of y=0.018 x-0.005. Hence Beer-Lmbert's law was obeyed.

Table : Calibration curve data of Perindopril in pH 6.8 phosphate buffer

Concentration	Absorbance
0	0
10	0.178
20	0.353
30	0.537
40	0.724
50	0.913

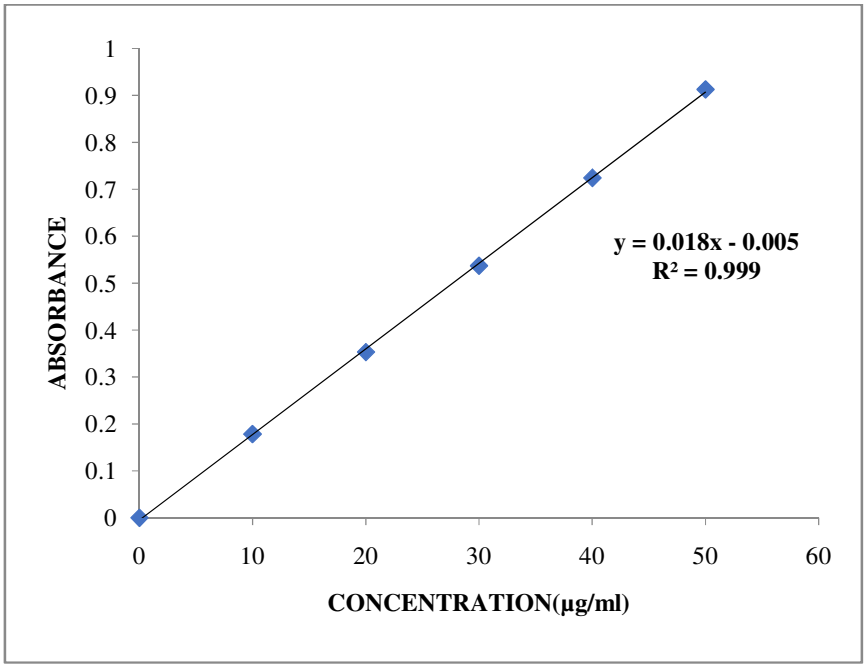

FIG : Calibration curve data of Perindopril in pH 6.8 phosphate buffer

EVALUATION OF PRE-COMPRESION PARAMETERS OF POWDER BLEND

Table: Evaluation of pre-compression parameters of powder blend

Formulation code	Angle of repose	Bulk density(gm/mL)	Tapped density (gm/mL)	Carr's index(%)	Hausner's ratio
F1	23.04 ±0.3	0.54 ±0.01	0.57 ±0.01	5.26 ±2.0	1.06 ±0.02
F2	23.77 ±0.4	0.55 ±0.01	0.59 ±0.02	6.78 ±2.0	1.07 ±0.03
F3	23.53 ±0.5	0.55 ±0.02	0.61 ±0.03	9.84 ±2.0	1.11 ±0.03
F4	23.37 ±0.4	0.53 ±0.03	0.58 ±0.04	8.62 ±2.2	1.09 ±0.03
F5	22.16 ±0.2	0.48 ±0.02	0.55 ±0.01	12.14 ±4.9	0.65 ±0.23
F6	23.44 ±0.4	0.50 ±0.01	0.58 ±0.01	14.96±2.2	1.17±0.03

F7	23.31±0.3	0.47 ±0.02	0.55±0.03	14.23±2.0	1.16±0.23
F8	22.83±0.4	0.43 ±0.03	0.50±0.02	13.2±2.0	1.15±0.02
F9	22.44±0.2	0.58 ±0.01	0.66±0.01	11.81±2.2	1.13±0.02

- For each formulation blend of drug and excipients were prepared and evaluated for various pre compression parameters described earlier in methodology chapter.
- The bulk density of all formulations was found in the range of 0.43 ±0.03 -0.58 ±0.01 and tapped density was in the range of 0.50±0.02 -0.66±0.01
- The Carr's index and Hausner's ratio was calculated from tapped density and bulk density.

EVALUATIONS OF POST COMPRESSION PARAMETERS OF PERINDOPRIL ODTs

Table: Evaluation of post compression parameters of Perindopril Fast dissolving tablets

Formulation codes	Average weight(mg)	Hardness (kg/cm^2	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* disintegration Time(sec)
F1	98.25	2.28	0.48	1.67	99.96	51
F2	99.68	2.45	0.39	1.61	97.21	46
F3	98.41	2.32	0.58	1.75	96.20	58
F4	100.02	2.25	0.35	1.58	99.35	24
F5	96.69	2.37	0.44	1.64	97.18	62
F6	97.47	2.48	0.51	1.89	98.65	55
F7	99.59	2.38	0.49	1.65	99.86	65
F8	98.23	2.46	0.47	1.77	98.41	57

F9	99.72	2.35	0.51	1.82	98.62	51

In vitro* disintegration time :In vitro* disintegration studies showed from 24-65 sec. The F4 formulation showed very less *in vitro* disintegration time i.e.44 sec.

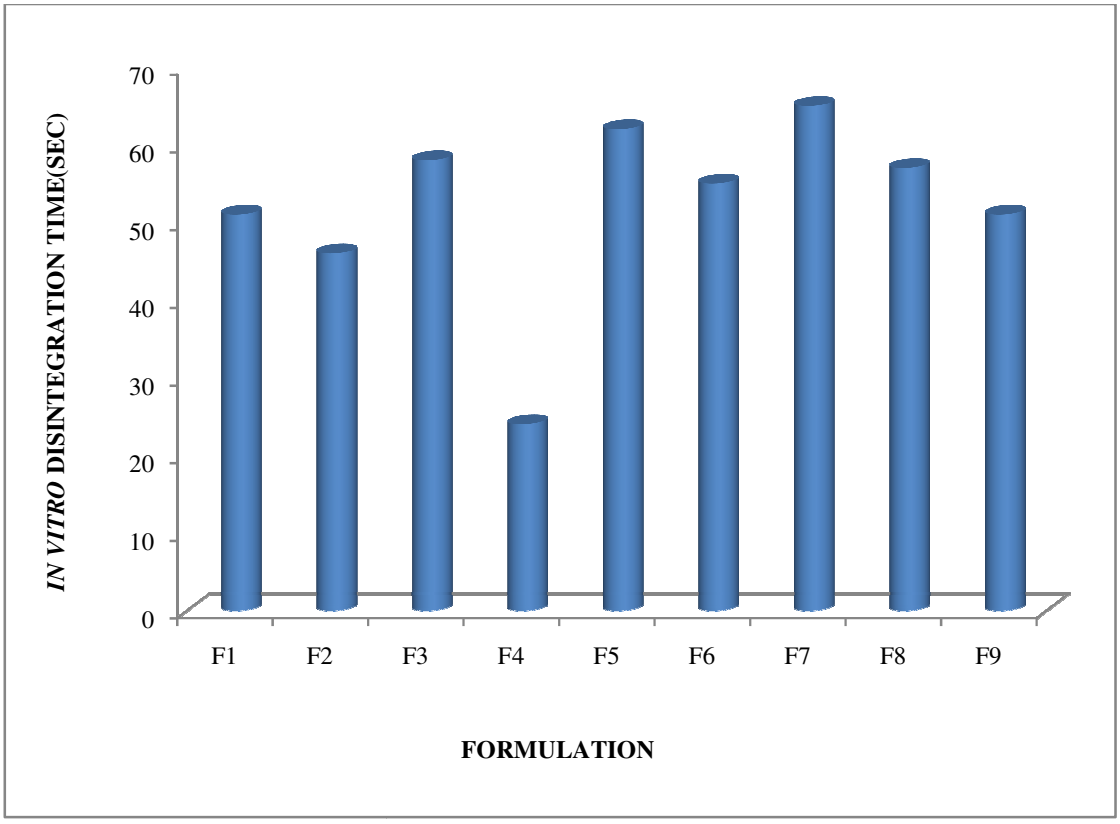

Figure : *In vitro* disintegration time

***IN VITRO* DRUG RELEASE SYUDIES OF PERINDOPRIL**

Table : *Invitro* Dissolution data of Perindopril

Time (mints)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	12.25	15.08	21.18	27.32	25.47	30.55	29.19	31.95	26.47
10	28.88	33.62	42.38	49.34	44.92	38.71	35.62	46.35	41.76
15	35.49	46.71	55.67	64.04	58.75	45.68	51.37	54.09	49.52
20	58.22	63.35	72.85	75.91	67.29	59.18	68.88	62.76	55.68

30	76.19	79.48	81.57	86.31	82.17	77.32	73.49	68.19	74.32
45	88.37	92.82	95.22	99.78	95.36	91.48	88.67	85.22	81.61

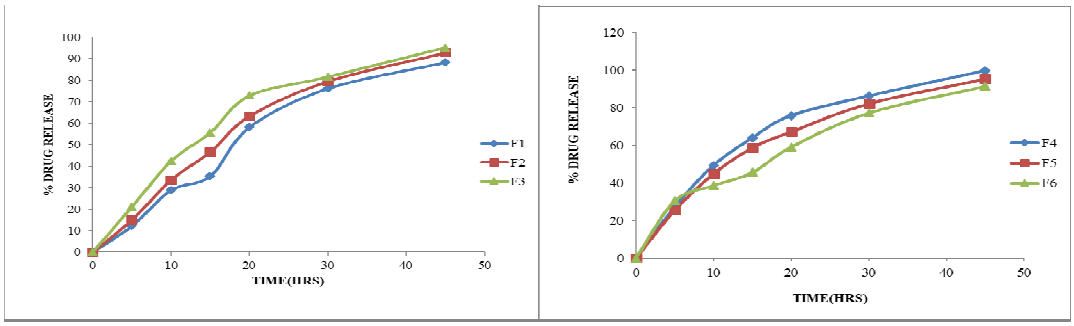

Fig: Dissolution profile of formulations F1, F2, F3Fig: Dissolution profile of formulations F4, F5, F6

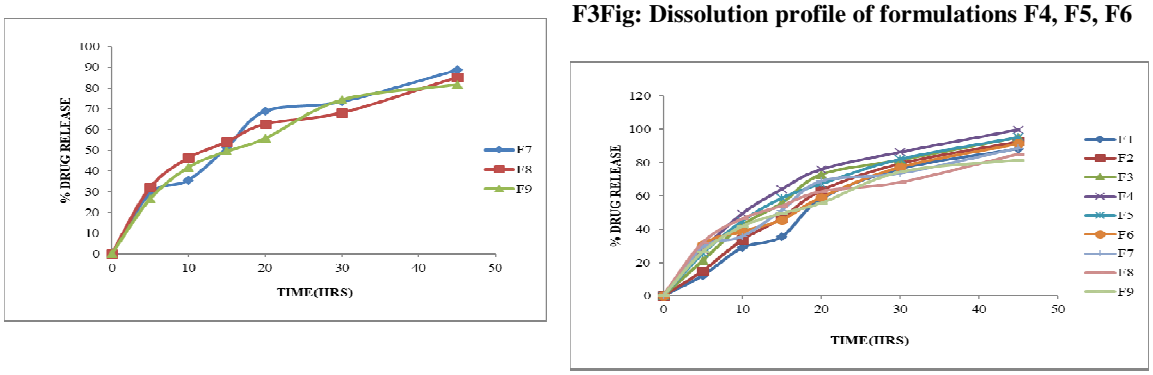

Fig: Dissolution profile of formulations F7, F8, F9Fig: Dissolution profile of all formulations F1-F9

From the Table it was evident that the formulations prepared with CroscarmelloseSodium powder were showed good drug release i.e.,95.22 % (F3 Formulation) in higher concentration of blend i.e. 12 mg. Formulations prepared with Crospovidone showed good drug release i.e., 99.78 % (F4 Formulation) in 4 mg concentration when increase in the concentration of Crospovidone drug release unable to retarded. Formulations prepared with Sodium starchglycolate showed maximum drug release i.e., 88.67 % (F7 Formulation) at 45 min in 4 mg of blend.

Among all formulations F4 formulation considered as optimised formulation which showed maximum drug release at 45 min. i.e. 99.78 %. CroscarmelloseSodium were showed good release when compared to Sodium starchglycolate.

Finally concluded that f4 formulation (contains Crospovidone) was optimised better formulation.

FTIR RESULTS :

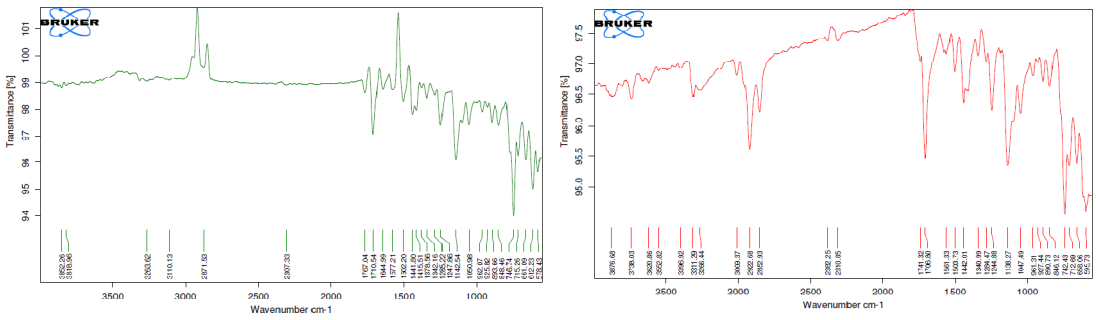

Fig : FTIR of Perindopril Pure DrugFig: FTIR of Perindopril optimized formulation

Perindopril was mixed with proportions of excipients showed no colour change providing no drug-excipient interactions

CONCLUSION

The Oral disintegrating tablets of Perindoprilwere formulated by using super disintegrants like Sodium Starch Glycolate, Cross Caramellose Sodium And Crosspovidone. FTIR study reveals that there is no drug-excipients interaction between Perindopril and excipients.The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. The use of super disintegrant Crospovidone at the concentration of 4 mg given better release of drug when compared to other superdisintegrants. The Optimised Formulation (F4) was showed Highest Drug Release (99.78%) in 45 minutes. The proposed ideal and reproducible characteristics of disintegration time and drug release profile.

By employing commonly available pharmaceutical Glycolate, Cross Caramellose Sodium And Crosspovidone and Lactose a fast disintegrating tablet of Perindopril can be developed which can be commercialized. The developed formulation of Perindopril ODT showed good efficacy, rapid onset of action, better patient compliance.

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