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Research Article

Formulation and evaluation of orodispersible Enalapril maleate tablets: A comparative study on natural super disintegrents and synthetic super disintegrents

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Abstract

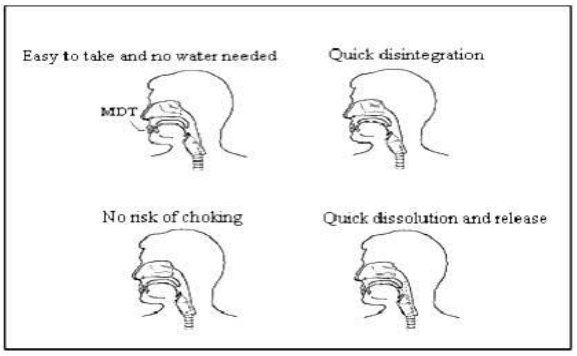
The aim of the present investigation is to formulate Enalapril maleate oral disintegrating tablet by using natural and synthetic super disintegrents. ODTs may also be used to deliver drugs to the oral cavity, for local action or, in some cases, absorption across the oral mucosa, thereby avoiding first-pass hepatic metabolism and potentially increasing the rate and extent of uptake, and reducing undesirable metabolites. The objectives of the research work is to formulate oral disintegrating tablets of Enalapril maleate by using different super disintegrates (Natural, Synthetic) in different ratio by direct compression technique and tablets were evaluated for pre compressional and post compressional Parameters such as angle of repose, bulk density, tapped density, compressibility index, drug content and in-vitro drug release study, hardness, friability, wetting time and *in vitro* dispersion time. To study the physical characteristics of the individual drug and optimized formulations by FTIR spectroscopy. To evaluate various characteristics of the resulting tablets. Formulation CCS3, IH2 were subjected to stability Studies as per ICH guidelines at temperatures and humidity of 25±5ºC/60±5%RH; and 40±5ºC/75±5%RH. Tablets didn't reveal any appreciable changes in respect to hardness, disintegration time, drug content and dissolution profile.

Keywords: ODTs, Enalapril Maleate, Super Disintegrants, Sodium starch Glycolate, Isphagula husk, Cross Povidone, MCC, Cross Carmellose Sodium

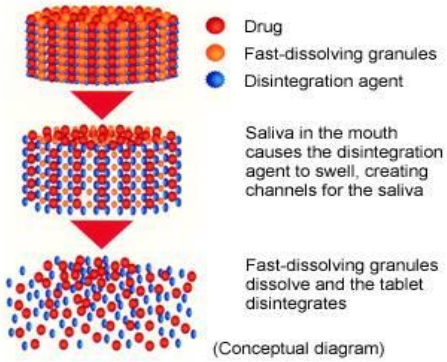
1. Introduction

1.1 Orally disintegrating tablets

The concept of Fast dissolving Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva [1]. The center for drug Evaluation and Research states an ODT to be: "A solid dosage form containing medicinal substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue."These tablets are distinguished from conventional, sublingual tablets, lozenges and buccal tablets which require more than a minute to dissolve in the mouth. In the literature these are also called orally disintegrating, Orodisperse, Mouth dissolving, Quick dissolving, Fast-melt and rapidly disintegrating tablets and freeze-dried wafers [2].



Disintegration Mechanism of ODT drugs



1.2 Mechanism of Action Enlapril:

Enalapril, after hydrolysis to enalaprilate, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, It results in small increases of serum potassium.

2. Materials and Methods

Pre gelatinized Starch(SD Fine, Mumbai), MCC (PH-102), Lactose anhydrous, Crospovidone, Sodium starch Glycolate, Magnesium stearate, Lactose, Cross Carmellose Sodium, Sodium Saccharin, Orange Flavor, Aerosil, Glyceryl behanate.

2.1 Equipments

Analytical balance, pH meter, Friability tester,Hardness tester, Disintegration Tester, Dissolution apparatus (Veego), UV-Visible spectrophotometer (Analytical), Compression machine(sixteen stationary rotary) (Cadmach), Bulk Density Tester.

2.2 Methodology

2.2.1 Extraction of Natural polymer from Ispaghula husk:

For the isolation of mucilage, seeds of *Plantago ovata* were used. They were soaked in distilled water for 48 h and then boiled for 1 h for complete release of mucilage into water. The material was filtered by squeezing in a muslin cloth to remove marc. Then equal volume of acetone was added to filtrate to precipitate the mucilage. The mucilage was separated and dried in oven at a temperature less than 60°C, powdered (#60 mesh), weighed and stored in desiccator until further use.

2.2.2 Preparation of Mixed blends of drug and excipients

All the ingredients were weighed accordingly specified in the formulation (table-8) and mixed well except magnesium stearate. Then the blend was passed through sieve no 60 which was used for the evaluation of flow properties.

2.2.3 Compression of Tablets

To the mixed blend of powder and excipients finally add magnesium stearate and then mixed for 5 min. The mixed blend was compressed with twelve (12) station tablet punching machine using 7 mm flat punches. The working formula was given in Table.No.1

3. Results and discussions

3.1 Evaluation of Pre compressional parameters

Bulk density

Apparent bulk density was determined by pouring the blend into a graduated cylinder [3]. The bulk volume (V_b) and weight of the powder was determined. The results were given in table.no.2

Bulk density = M / V_b

Tapped density

The measuring cylinder containing a known mass of powder blend was tapped for a fixed number of times as per USP apparatus-II. The minimum volume occupied by the powder after tapping was measured. The results were given in table.no.2

Tapped density = weight/tapped volume

Compressibility index

Compressibility index is calculated as follows. The results were given in table.no.2.

Tapped density- Bulk density/ Tapped density*100

The value below 15% indicates a powder with good flow characteristics where as above 25% indicates poor flow ability [4].

Haussner's ratio

It is an indirect index of ease of powder flow, it is calculated as follows.

Tapped density / Bulk density

Haussner's ratio <1.25 indicates good flow properties, where as >1.5 indicates poor flowability. The results were given in table.no.2.

Angle of Repose

Angle of repose was determined using funnel method. The blend was poured through funnel that can rise vertically until a maximum cone height (h) was obtained. Radius of the heap(r) was measured and angle of repose was calculated as follows [5]. The results were given in table 2.

$$Ø = \tan^{-1} h/r$$

3.2 Evaluation of tablets

All the prepared tablets were evaluated for the following parameters as per the I.P guidelines.

Weight variation

Twenty tablets from each formulation were selected randomly and average weight was determined. Individual tablets were then weighed and compared with average weight [6,7]. The results were given in table.no.3.

Hardness test

The force required to break a tablet in a diametric compression was determined by using Pfizer tablet hardness tester. The results were given in table.no.3.

Friability

The weight of twenty tablets was noted and placed in the friabilator and then subjected to100 revolutions at 25 rpm. Tablets were dedusted using a soft muslin cloth and reweighed [8,9]. The results were given in table.no.3.

Percent friability = [initial weight – final weight / initial weight] × 100

Wetting time and Water absorption ratio

A piece of paper folded twice was kept in a petri dish (internal diameter 6cms) containing 6ml of purified water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was weighed. Water absorption ratio, R was determined using the following equation [10]. The results were given in table.no.3.

$$R = [Wa – Wb / Wb] \times 100$$

where Wa, Wb are the weights of tablets before and after wetting.

***In vitro* dispersion time**

Tablet was added to 10ml of distilled water at 37± 0.5˚C, time required for complete dispersion of tablet was measured [11,12]. The results were given in table.no.3.

Drug content uniformity

The drug content uniformity was determined by taking the powder equivalent to 10mg, then it was (n=3) dissolved in P^H6.8 phosphate. Required dilution (10µg/ml) was prepared and absorbance was taken against the blank at 206nm. The results were given in table.no.3.

***In vitro* disintegration time**

The disintegration was performed using an I.P 85 disintegration apparatus with distilled water at 37±0.5 ˚C. The time taken for disintegration of all formulations was noted in table 4.

3.3 Dissolution studies

Dissolution rate of Enalapril maleate from all formulations was performed using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with paddle. The dissolution fluid was 900 ml of P^H6.8 phosphate buffer with a speed of 50 rpm and temperature of 37±0.5˚C were used in each test. 5 ml of sample was withdrawn at different time intervals (2.5, 5, 10, 15 & 20 mins) and fresh medium was replaced to maintain sink conditions. The samples are analysed by using UV- Visible spectrophotometer at λ_{max} 205 nm. Dissolution studies were performed in triplicate and the results were shown in table.no.5. We were plotted a graph by taking time on x-axis and % cumulative drug release on y-axis. The graphs were represented in fig. no. 1-4.

3.4 Stability studies

The stability studies were conducted for optimized formulations at 25˚C / 60%RH and 40˚C / 75% RH. For these formulations we were reconducting the wetting time, disintegration time and dissolution time [13,14].

3.5 Characterization of Enalapril maleate tablets:

FTIR studies

The drug- excipients interaction was studied using FTIR. IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer using KBr pellet technique [15,16]. This spectra was scanned over the 3600 to 500 cm^{-1} range. The polymers should not show any change on the functional groups of enalparil maleate. The values were mentioned in the table 6. The IR spectras of pure drug and optimized formulations were showed in fig. no. 5-8.

Table 1: Formulation of oral disintegrating tablets of Enalapril maleate

Ingredients (mg per tablet)	CCS1	CCS2	CCS3	SSG1	SSG2	SSG3	CP1	CP2	CP3	IH1	IH2
Enalapril maleate	10	10	10	10	10	10	10	10	10	10	10
Lactose Anhydrous	80	80	80	80	80	80	80	80	80	80	80
MCC PH-102	48.5	44	41	48.5	44	41	48.5	44	41	48.5	44
Cros Carmellose Sodium	4.5	9	12	---	---	---	---	---	---	---	---
Sodium Starch Glycollate	---	---	---	4.5	6	12	---	---	---	---	---
Crospovidone	---	---	---	---	----	---	4.5	6	12	---	---
Ispaghula Husk Powder	---	---	---	---	---	---	---	---	---	4.5	6
Sodium Sacharin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Orange flover	1	1	1	1	1	1	1	1	1	1	1
Aerosil	3	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Glyceryl Behanate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight	150	150	150	150	150	150	150	150	150	150	150

CCS - Croscarmellose Sodium; SSG - Sodium Starch Glycollate; CP – Crospovidone; IH - Ispaghula Husk Powder

Table 2: Evaluation of flow properties of the blend

Formulations	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio	Flow ability
CCS1	33	0.56	0.65	13.84	1.16	Fair
CCS2	32	0.57	0.64	13.62	1.1	good
CCS3	35	0.66	0.76	10.2	1.17	Excellent
SSG1	28	068	0.74	13.12	1.14	good
SSG2	32	0.54	0.62	12.14	1.12	good
SSG3	29	0.65	0.71	8.02	1.11	good
CP1	36	0.67	0.75	17.8	1.16	Excellent
CP2	35	0.54	0.65	11.25	1.19	Excellent
CP3	28	0.61	0.71	10.6	1.21	Excellent
IH1	38	0.59	0.63	7.8	1.09	good
IH2	36	0.68	0.75	11.1	1.12	good

Table 3: Quality control tests for the oral disintegrating tablets of enalapril maleate

Formulations*	Average Weight*	Hardness *Kg/cm^2	Friability *(%)	Wetting time*	Water absorption ratio*
CCS1	149±0.12	3.6±0.11	0.481±0.16	11.12±0.21	39±0.14
CCS2	150±0.21	3.6±0.24	0.56±0.17	10.13±0.34	28±0.15
CCS3	**151.3±1.8**	**3.5±0.49**	**0.57±0.17**	**8.55±0.15**	**34±0.24**
SSG1	149.5±0.25	3.9±0.11	0.31±0.16	16.87±0.16	38±0.16
SSG2	148.9±0.54	3.8±0.14	0.46±0.19	14.76±0.19	40±0.14
SSG3	150±0.01	3.9±0.17	0.41±0.24	15.41±0.13	38±0.18
CP1	149±0.19	3.9±0.21	0.54±0.21	22.13±0.77	42±0.19
CP2	148±0.71	3.7±0.15	0.52±0.27	20.14±0.14	44±0.28
CP3	150±0.76	3.7±0.17	0.41±0.15	18.76±0.21	47±0.14
IH1	147±0.16	3.8±0.2	0.31±0.16	13.12±0.13	51±0.13
IH2	**149.4±0.87**	**4.0±0.32**	**0.295±0.22**	**11.56±0.12**	**54±0.17**

Table 4: Quality control tests for the oral disintegrating tablets of enalapril maleate

Formulations*	Disintegration time * (sec)	Drug content* (%)	Percentage Drug Dissolved After 10 min*.	*In vitro* Dispertion time* (s)
CCS1	14.25±0.45	102.21±0.73	89.24±0.42	15±0.22
CCS2	13.51±0.71	98.97±0.12	91.21±0.31	13±0.65
CCS3	**10.64±0.61**	**99.58±0.53**	**97.24±0.86**	**11±0.72**
SSG1	54.21±0.14	97.25±0.62	87.24±0.68	61±0.25
SSG2	56.85±0.32	98.21±0.54	91.25±0.45	59±0.36
SSG3	57.21±0.68	98.56±0.41	91.35±0.76	59±0.62
CP1	38.25±0.21	94.95±0.25	84.91±0.13	51±0.98
CP2	37.65±0.24	96.78±0.61	88.24±0.95	50±0.57
CP3	39.78±0.32	98.8±0.32	95.42±0.42	51±0.24
IH1	12.24±0.45	98.25±0.23	97.21±0.68	11±0.57
IH2	**10.24±0.55**	**99.6±0.4**	**98.21±0.9**	**10±0.32**

Table 5: Dissolution profile of the oral disintegrating tablets of enalapril maleate

Formulations	Cumulative % drug dissolved (mins)					
	0	**2.5**	**5**	**10**	**15**	**20**
CCS1	0	37.6±0.26	60.24±0.35	79.25±0.92	91.25±0.24	98.47±0.31
CCS2	0	41.25±0.12	62.25±0.95	81.54±0.7	89.350.89	97.28±0.71
CCS3	**0**	**50.24±0.21**	**71.26±0.31**	**85.45±0.12**	**91.78±0.21**	**99.12±0.11**
SSG1	0	44.2±3.16	59.21±0.24	78.4±0.12	89.9±0.1	95.24±0.21
SSG2	0	43.21±0.14	60.21±0.1	75.26±0.21	88.7±0.31	96.25±0.14
SSG3	0	43.8±2.3	69.35±0.35	78.98±0.26	91.36±0.32	94.27±0.12
CP1	0	39.8±1.26	67.2±0.54	79.28±0.11	90.4±0.12	93.14±0.78
CP2	0	41.6±0.51	68.5±0.32	75.9±0.64	88.6±0.85	95.7±0.74
CP3	0	43.7±2.5	60.35±0.12	75.44±0.46	88.69±1.3	97.25±0.2
IH1	0	45.26±0.2	69.24±0.21	81.24±0.3	89.19±0.2	97.02±0.13
IH2	**0**	**49.12±0.74**	**70.26±0.1**	**85.29±0.3**	**91.42±0.6**	**99.7±0.1**

Fig 1: Comparative dissolution profile of Enalapril maleate tablets containing different concentrations of cros carmellose sodium as super disintegrant.

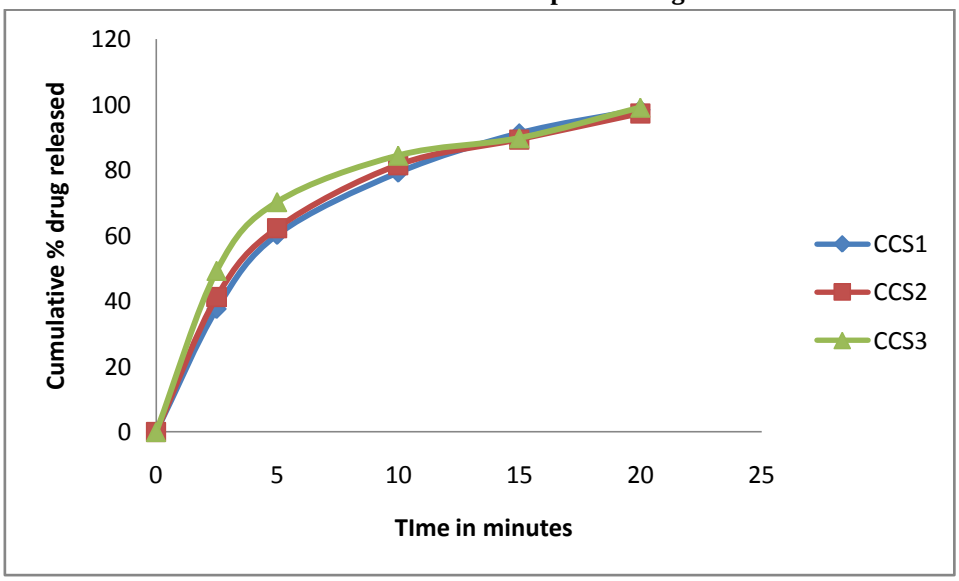


Fig 2: Comparative dissolution profile of Enalapril maleate tablets containing different concentrations of sodium starch glycollate as super disintegrant

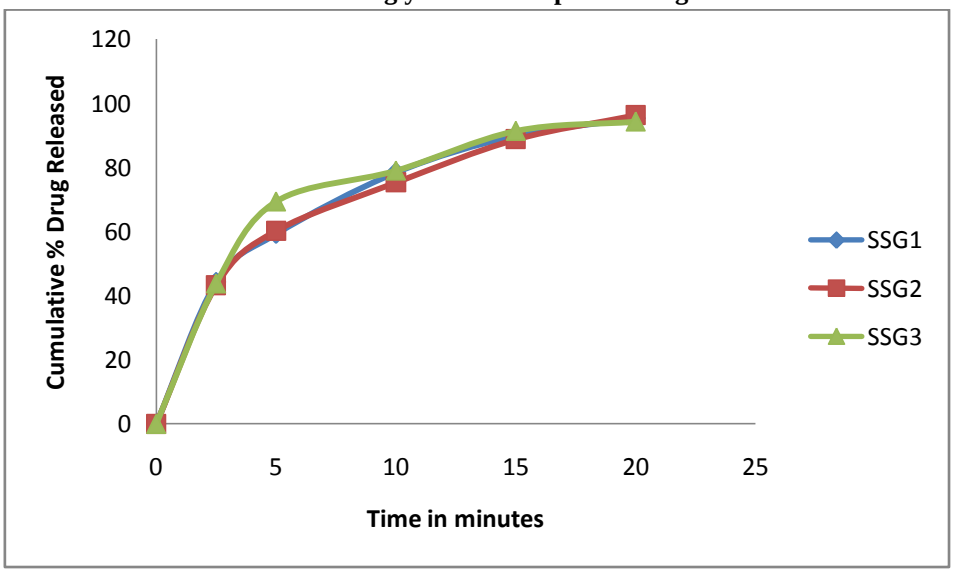


Fig 3: Comparative dissolution profile of Enalapril maleate tablets containing different concentrations of cross povidone as super disintegrant

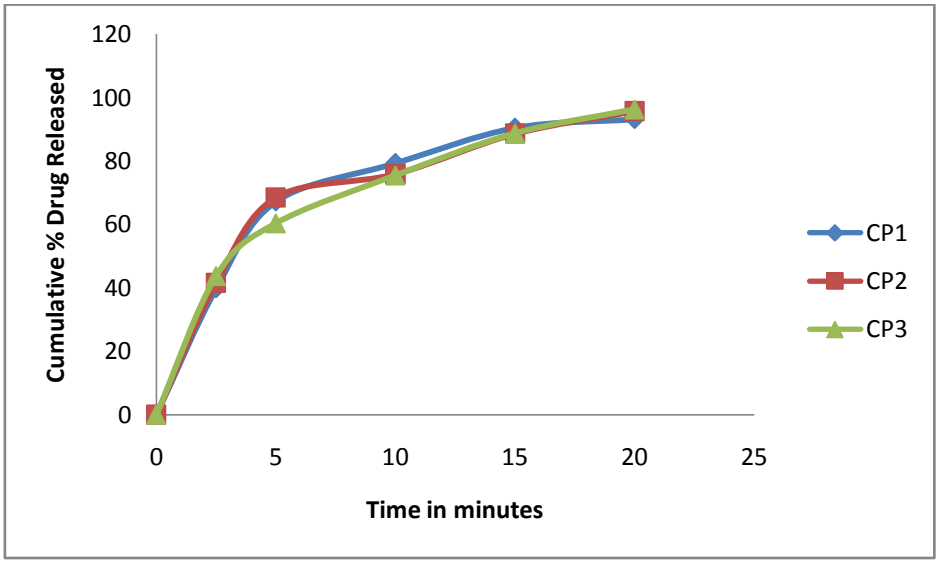


Fig 4: Comparison of dissolution profiles of Enalapril maleate tablets containing different concentrations of Ispaghula husk powder as a natural super disintegrant

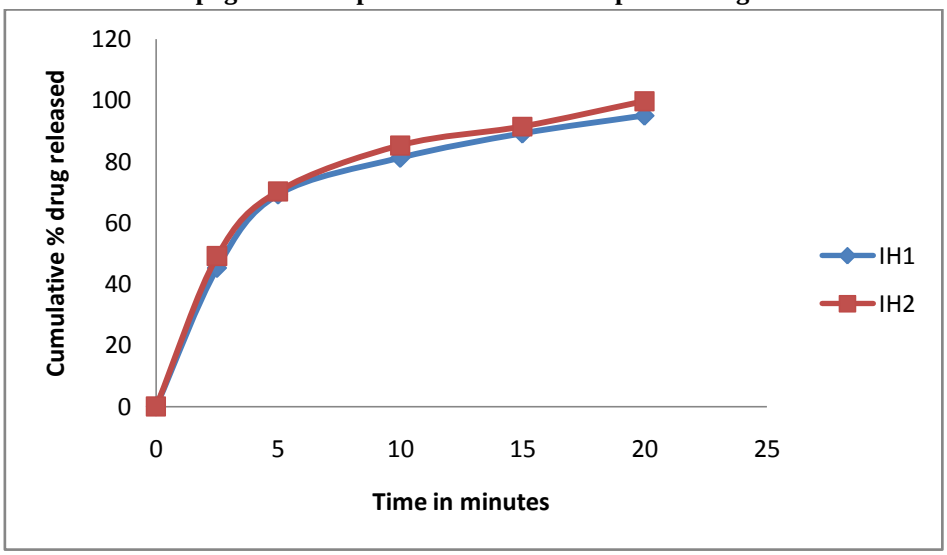


Fig 5: Comparison of dissolution profiles of optimized formulations CCS3 & IH2

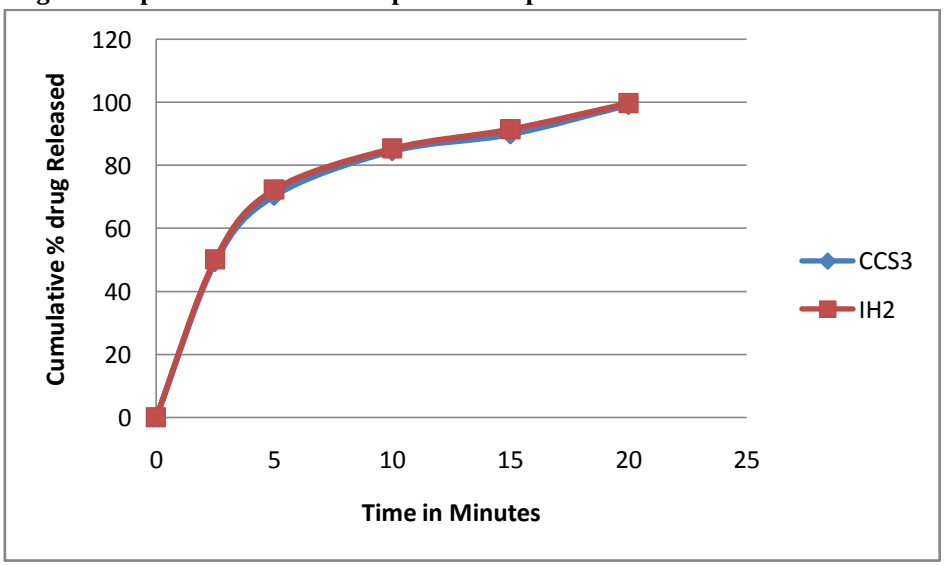
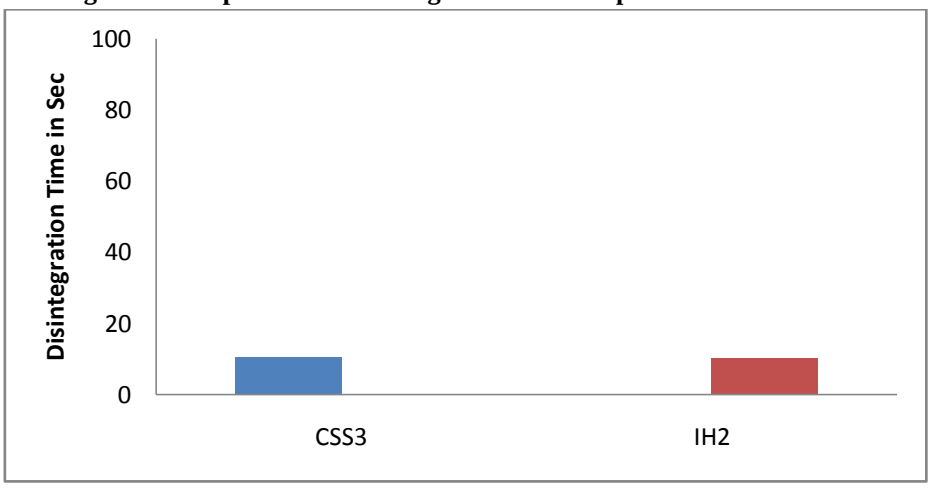


Fig no.6: Comparision of disintegration time of optimized formulations



FTIR Studies:

Fig.7: FTIR of enalapril maleate (pure drug)

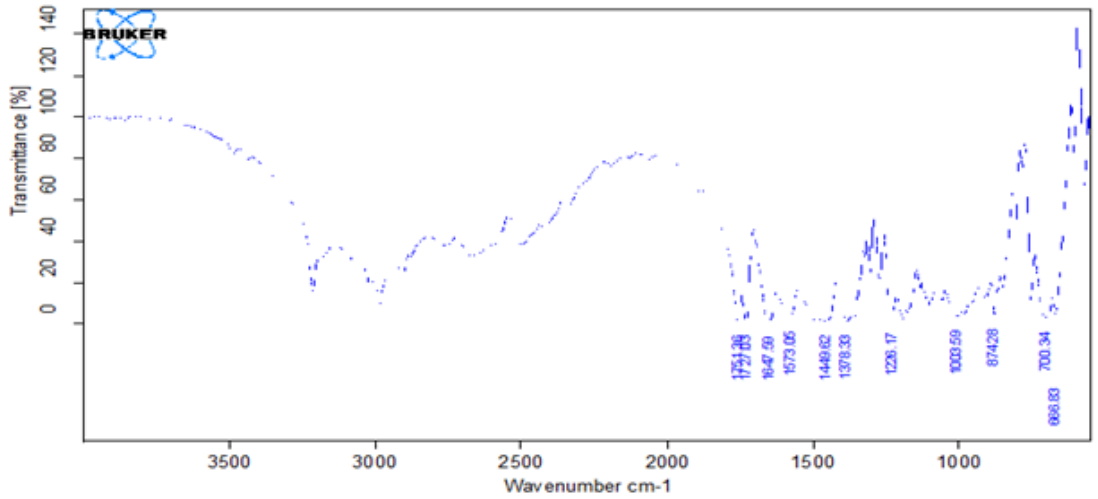


Fig 8: FTIR of formulation CSS3

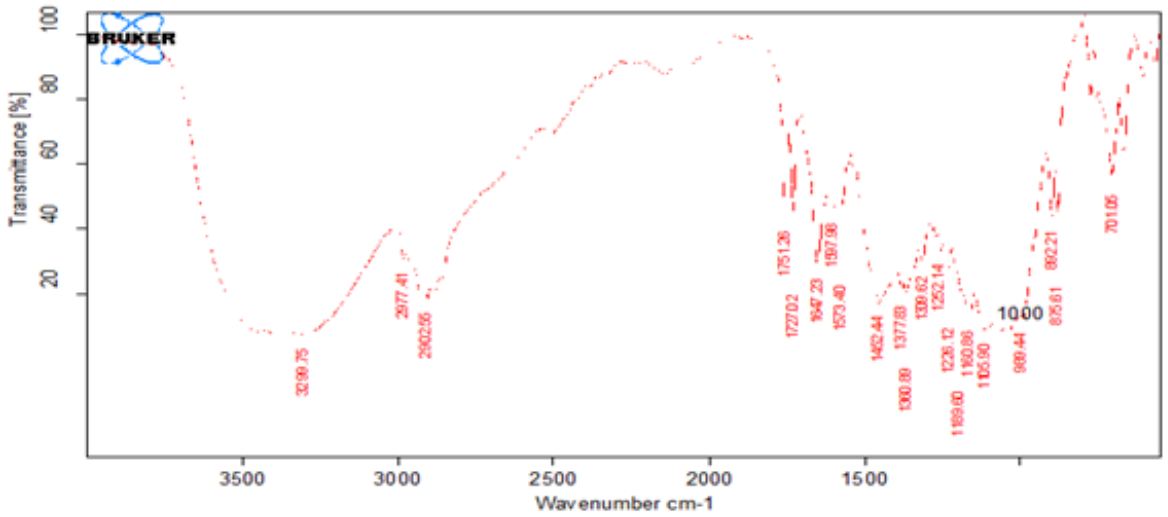


Fig 9: FTIR of formulation IH2

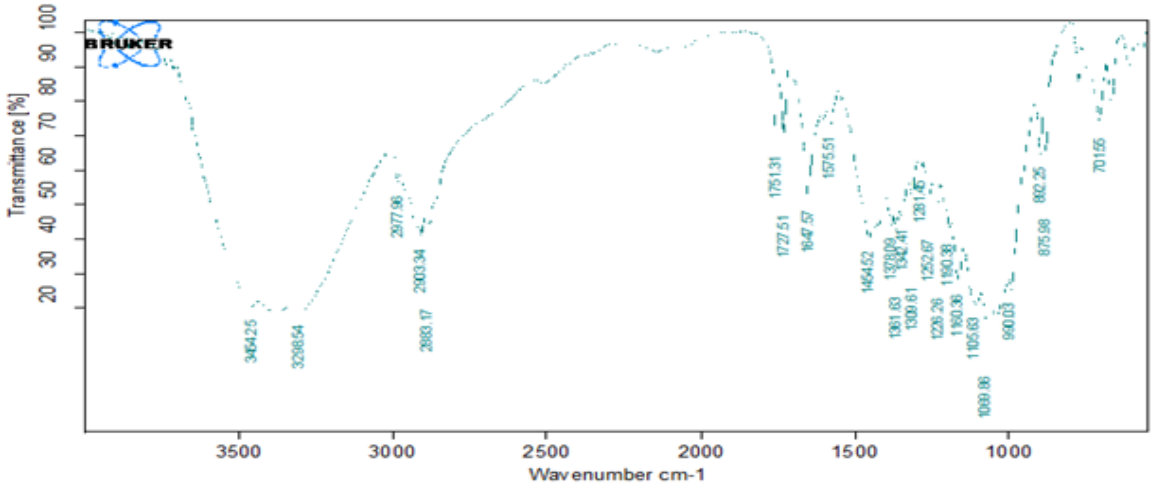


Table 6: FTIR values of Optimized Formulations

Material	Peak	Functional group
Pure API	3274.34	NH group
	1751.36	C=O in esters
	1727.03	C=O in acids
	1647.59	C=O in amides
Formulation CCS3 (Drug:CCS)	3299.75	NH group
	1751.26	C=O in esters
	1727.02	C=O in acids
	1647.23	C=O in amides
Formulation S2 (Drug : Isphagula husk)	3298.54	NH group
	1751.31	C=O in esters
	1727.51	C=O in acids
	1647.57	C=O in amides

Stability analysis:

Table No 7: Stability Analysis of Optimized Formulations

Formulation	No of days	25˚C & 60%RH		40˚C &75% RH	
		Wetting time(s)	Disintegration time(s)	Wetting time (s)	Disintegration time (s)
CCS3	0	8.47±0.124	10.68±0.226	8.47±0.225	10.68±0.146
	15	8.45±0.148	10.65±0.446	8.45±0.256	10.61±0.228
	30	8.48±0.346	10.66±0.424	8.46±0.154	10.59±0.446
	45	8.43±0.146	10.64±0.568	8.44±0.654	10.62±0.356
	60	8.44±0.214	10.62±0.146	8.43±0.168	10.64±0.186
IH2	0	11.56±0.146	10.02±0.148	11.56±0.983	10.02±0.146
	15	11.54±0.566	9.98±0.167	11.53±0.156	10.0±0.264
	30	11.50±0.354	9.99±0.964	11.51±0.256	9.97±0.446
	45	11.51±0.446	9.98±0.843	11.54±0.140	9.99±0.356
	60	11.49±0.176	9.97±0.116	11.50±0.146	9.98±0.264

Drug content:

Formulation	No of days	25˚C / 60%RH		40˚C / 75% RH	
		Drug content	Dissolution	Drug content	Dissolution
CCS3	0	99.08±0.86	-	99.08±0.86	-
	15	98.12±0.56		98.75±0.23	
	30	98.74±0,24		98.06±0.36	
	45	98.38±0.328		97.86±0.28	
	60	98.25±0.156		97.54±0.442	
IH2	0	98.6±0.24	-	98.6±0.86	-
	15	98.24±0.168		98.36±0.52	
	30	98.36±0.264		98.12±0.16	
	45	98.14±0.188		97.56±0.34	
	60	98.08±0.22		97.24±0.28	

4. Conclusion

The present work led to the development of orodispersible tablets of enalapril maleate by using different concentration of natural and synthetic superdisintegrents. The prepared oral disintegrating tablets of enalapril maleate were found to be good in appearance without cracking, lamination and chipping. The promising formula (CCS3, IH2) have showed fast disintegration and displayed *in vitro* dispersion time of 11 s and 10.5's. The dissolution rates of the optimized formulations (CCS3, IH2) were found to be good. Among the promising ODT formulation CCS3, IH2 the formula IH2 was found to be superior when compared to formulation CCS3 since formulation CCS3 used natural disintegrant (i.e 6%w/w iaphagula husk) at a lower concentration than the formulation CCS3 (8%w/w cros carmellose sodium) , and hence it is found to be more cost effective. The FTIR studies were also showed the there was no interaction between drug and polymer. The stability study was done for 3 months all parameters such as wetting time, disintegration time, drug content and *in-vitro* dissolution studied at the end of every month, the results shows that no significant changes in that parameters.

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References

[1] Lachman L; Liberman H. and Kanig J; The theory and Practice of Industrial Pharmacy;Third edition: 293-345,346-373.

[2] Swarbrick J. and Boylan J; Encyclopedia of Pharmaceutical Technology; Volume 14: 345-348,385-400,401-418.

[3] Taylor and Francis; International Journal of Toxicology: Toxicity of excipients - A food and drug administration perspective; 2003; 22(5):377-380.

[4] Chowhan Z; Pharmaceutical Technology: Excipients and their functionality in drug product development; 1993; (9).

[5] Lachman L; Liberman L. and Schwartz J; Pharmaceutical Dosage Forms: tablets; Second Edition: Volume I.

[6] Banker G. and Rhodes C; Drug and Pharmaceutical Sciences: Modern Pharmaceutics; Third edition; Volume 2:333-394.

[7] Swarbrick J and Boylan J; Encyclopedia of Pharmacutical Technology; 7: 121-160.

[8] Seager H.Drug delivery products and the zydis fast dissolving dosage forms, *J.Pharm.Pharmacol*. 1998, 50(4), 375-382.

[9] Indurwade, N. H., Rajyaguru,T. H. and Nakhat, P.D., Fast Dissolving drug delivery systems: A Brief overview**,** *Indian Drugs*, 2002, 39(8), 405-09.

[10] Devrajan,P.V,Gore, S.P., Fast Dissolving Tablets: The Future Compaction**,** *Express Pharma Pulse*, 2000: 23, 7(1), 16.

[11] Habib W, Khankari R, Hontz J., "Fast-dissolving Drug Delivery Systems**",** *Critical Reviews* ^{TM} *Therapeutic Drug Carrier Systems***,** 2000, 17(1), 61-72.

[12] Kuchekar, B.S., Badhan, A.C., Mahajan, H.S., Fast Dissolving drug delivery systems: A brief overview, *Pharma Times*, 2003, 35, 7-9.

[13] Reddy, L. H., Ghose, B. and Rajneesh, Fast Dissolving drug delivery systems: A brief overview, *Indian J. Pharm. Sci***.**, 2002, 64(4): 331-336.

[14] Parakh, S.R. and Gothoskar, A.V., Fast Dissolving drug delivery systems: A brief overview, *Pharma Tech* 2003, 92- 100.

[15] Lalla, J.K. and Sharma, A H. *Indian Drugs***,** 1994, 31(11), 503-508.

[16] Nail, S L. and Gatlin, L.A., In; Freeze drying: Principles and Practice, in Pharmaceutical Dosage Forms-Parenteral Medications, 2, 1993,163.