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Design and Characterization of Sublingual Tablets of Prochlorperazine Maleate by Natural and Synthetic Superdisintegrants

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ABSTRACT

Sublingual administration of the drug is known as placement of the drug under the tongue and drug reaches directly in to the blood stream. The concept of formulating sublingual tablets of Prochlorperazine maleate offers suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristic. Bitter taste of Prochlorperazine maleate was masked by inclusion complex with β-cyclodextrin and then sublingual tablets were prepared using various natural superdisintegrants such as hibiscus-rosa and fenugreek and synthetic superdisintegrants like Indion 414 and kyron T-314 in different concentrations by direct compression method. Prepared tablets were subjected to different evaluation parameters such as hardness, thickness, friability, weight variation, drug content uniformity, *in-vitro* disintegration time, water absorption ratio, wetting time, *in vitro* dissolution studies and stability studies are carried out by using best formulation. Overall, formulation F3 (10 mg of Indion 414) and F9 (10 mg of Hibiscus-rosa) based on disintegration time, wetting time and drug release were found to be an excellent formulations. Hence It was found that there was no significant difference between F3 and F9, which shows that natural superdisintegrants (10 mg of Hibiscus rosa) is as good as synthetic superdisintegrants (10 mg of Indion 414). Hence it proves that synthetic disintegrant can be replaced by natural disintegrants due to easy availability and compatibility.

Keywords: Prochlorperazine maleate, β-cyclodextrin, Indion414, Kyron T-314, Hibiscus rosa, Fenugreek

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INTRODUCTION

The oral route remains the preferred route for the administration of therapeutic agents due to low cost, ease of administration and high level of patient compliance. However, significant barriers impose for the oral administration of drugs, such as hepatic first pass metabolism and drug degradation within the gastrointestinal (GI) tract prohibiting the oral administration of certain classes of drugs especially biologics e.g. peptides and proteins. Consequently, other absorptive mucosal are being considered as potential sites for drug administration including the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity. These transmucosal routes of drug delivery offer distinct advantages over peroral administration for systemic drug delivery such as possible bypass of the first pass effect and avoidance of pre-systemic elimination within the GI tract.[1]

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularized, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, by passing the gastrointestinal tract and first-pass metabolism in the liver. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug.[2]

Drug delivery via sublingual mucous membrane is considered to be a promising alternative to the oral route. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid intake/diets have difficulties in swallowing these dosage forms. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and braciocephalic vein and then drained in to systemic circulation.

The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in

the oral cavity.[3]

Prochlorperazine maleate is a phenothiazine antipsychotic and widely used in prevention and treatment of nausea, vomiting including that associated with migraine or drug induced emesis.[4] The concept of formulating sublingual tablets of Prochlorperazine maleate offers suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristic and to know the effect of natural and synthetic superdisintegrants.

Advantages of Sublingual Tablets

- A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
- Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.
- Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g. asthma.
- Rapid absorption and higher blood levels due to high vascularisation of the region and therefore particularly useful for administration of anti-anginal drugs.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

MATERIALS AND METHODS

Materials

Prochlorperazine maleate and β-cyclodextrin were obtained from Yarrow chemical Mumbai, India. Kyron T-314 was obtained as gift sample from Ion Exchange India Ltd, Mumbai, India. Indian 414 was obtained as gift sample from Corel Pharma, Ahmedabad, India. All other chemicals used were of suitable analytical grade.

Methods

Preparation Of PCZM –B cyclodextrin Inclusion Complex to Mask Bitter Taste of Drug[5]

PCZM - βcyclodextrin inclusion complex were prepared by kneading method in 1:1 and 1:2 ratios. β-cyclodextrin and small quantity of distilled water was added in mortar with trituration to

get slurry like consistency. Then slowly drug was incorporated into the slurry and trituration continued further for 15 min. Slurry was further air-dried at 40ºC for 24 hours, pulverized and passed through sieve No. 100 and was stored in a dessicator over fused calcium chloride.

Taste Evaluation[6]

Taste evaluation was carried out by sensory test on healthy volunteers, with their prior consent

- Selection of volunteers- 5 healthy volunteers selected from age group of 20 to 30.
- Standard – Prochlorperazine maleate
- Test – Prochlorperazine maleate inclusion complex
- Sample Delivery method- Each volunteer
- Received all ratio in 4 hr after morning breakfast in 1 day.
- Scale of measurement- Taste Evaluation starts immediately after administration and continued for upto 15 secs. The scale used a ranking system from +++ tasteless to -- Extremely bitter.

PREFORMULATION STUDIES OF POWDER BLEND[7,8]

Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$$\tan(\theta) = h / r$$

Where, θ is the angle of repose

h is the height in cm.

r is the radius in cm.

Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is given by

$$D_b = M / V_b$$

Where, M is the mass of powder**,** V_b is the bulk volume of the powder.

Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder.

$$D_t = M / V_t$$

Where, M is the mass of powder , $V_t$is the tapped volume of the powder.

Hauser's ratio:

Hauser's ratio is an indirect index of ease of powder flow.

$$\textbf{Hauser's ratio} = D_t / D_b$$

Where, Dtis the tapped density., D_b is the bulk density.

Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is given by

$$I = (D_t - D_b / D_t) \times 100$$

Where, D_t is the tapped density of the powder , D_b is the bulk density of the powder.

Preparation of Tablets by Direct Compression Method

The Inclusion complex equivalent to 5 mg of drug was taken. Then it mixed with directly compressible diluents and superdisintegrant in a plastic container. Aspartame, Magnesium stearate and talc were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend.

Tablet compression:

The tablets were compressed by using single-station tablet punching machine. The compressible weight of each tablet was 100 mg. The tablet was compressed using 6 mm flat-faced punches. The hardness was adjusted to 2.5 to 3.0 kg/cm^2.

EVALUATION OF SUBLINGUAL TABLETS[9,10,11]

Weight variation:

The procedure described in Indian Pharmacopoeia (IP, 1996) was employed to determine the weight variation of the tablets. Twenty tablets were randomly selected from each batch and weighed on an electronic balance and mean weight was taken. Each tablet was then weighed individually and standard deviation in weight was calculated for each batch.

Hardness:

Five tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester. The mean values and standard deviation for each batch were calculated.

Thickness:

Dimension of the tablets was measured by using a calibrated dial caliper. Three tablets of each formulation were picked out randomly and its thickness was measured individually

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the

combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = (W_{initial} - W_{final}/W_{initial}) \times 100$$

***In-vitro* Disintegration time:**

The *in-vitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Wetting time:

Wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^{o}C. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

Water Absorption Ratio:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

$R = 100 \times Wa - Wb/Wa$

Where, Wa = Weight of tablet after water absorption Wb = Weight of tablet before water absorption.

***In-vitro* drug release:**

In-vitro Release of the drug was determined by estimating the dissolution profile.USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm. Phosphate buffer 6.8 was used as a dissolution medium at 37±0.5°C temperature. Determination of amount of drug dissolved form tablets was carried by UV spectrophotometer at 254 nm. In this test, single tablet from each formulation was used for the studies. At specified time intervals, 5 ml samples were collected and immediately replaced with an equal volume of fresh medium. Samples were analyzed by using UV spectrophotometer at 254 nm

RESULTS AND DISCUSSION

In the present study, initially bitter taste of Prochlorperazine maleate was masked by inclusion complex with β-cyclodextrin. All the ratios were tasted and the inclusion complex ratio 1:2 completely masked the bitter taste of the drug hence the 1:2ratio was taken for the formulation of sublingual tablets.

Standard graph of Prochlorperazine maleate was taken in Phosphate buffer 6.8, the absorption maxima was found at 254 nm.

The FT-IR spectra of drug and excipients showed that there was no interaction between them. The FT-IR spectra was shown in figure 1-4 and the spectral range was shown in table.1

Table 1 Comparison of FT-IR spectra of Pure drug and Excipient.

Description	**Pure drug (cm^{-1})**	**Drug+βcyclodextrin**	**I.C of PCZM + Indion 414 (cm^{-1})**	**I.C of PCZM + Kyron T-314(cm^{-1})**	**I.C of PCZM+ Hibiscus rosa(cm^{-1})**	**I.C of PCZM + Fenugreek (cm^{-1})**
$-CH_3$	2873.42	2872.45	2872.45	2872.45	2872.45	2872.45
$-CH_2$	2973.70	2972.73	2975.62	2979.48	2973.62	2972.73
Aromatic =CH	3007.44	3008.41	3007.44	3008.41	3008.41	3008.41
C-N	1357.64	1358.6	1357.64	1357.64	1357.64	1357.64
C-S	755.95	754.03	754.99	744.38	755.95	755.95
C=O	1693.19	1691.27	1694.16	1697.05	1691.27	1691.27
C-O-C	1280.50	1578.57	1280.50	1278.57	1280.50	1280.50
C-Cl	659.53	657.607	660.50	660.50	657.60	650.85
C=C	1619.91	1619.91	1619.91	1619.91	1619.91	1619.91

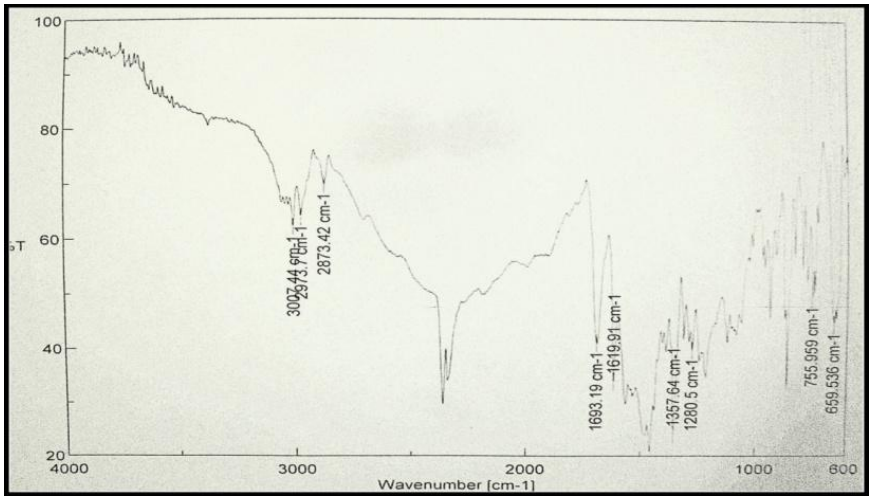

Figure 1 FT-IR spectrum of Prochlorperazine maleate

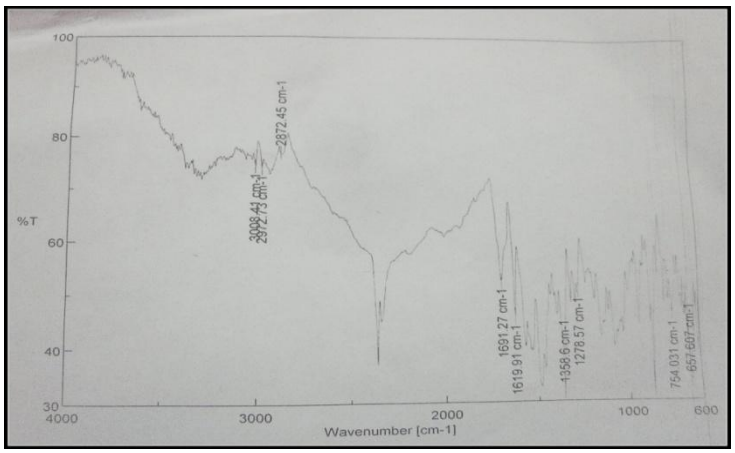

Figure. 2 FT-IR spectrum of PCZM + β-cyclodextrin

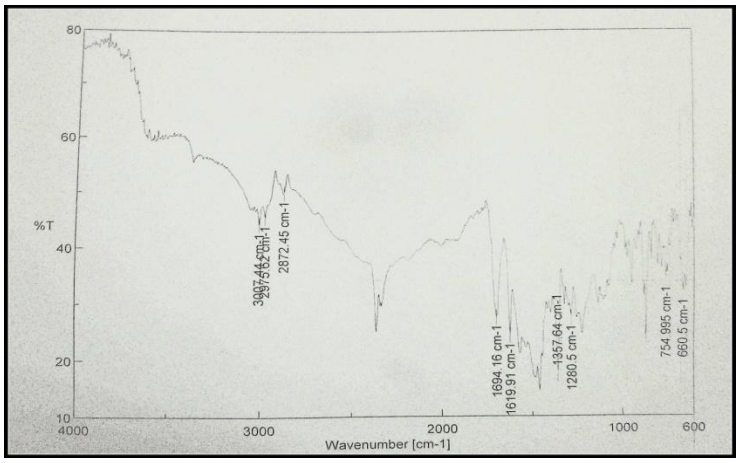

Figure 3 FT-IR spectrum of Inclusion complex of PCZM+ Indion414

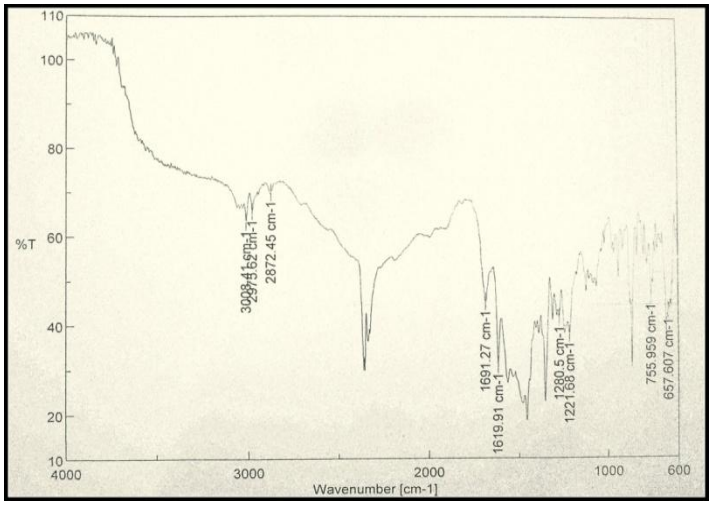

Figure 4 FT-IR spectrum of Inclusion complex of PCZM+ Hibiscus rosa

preformulation study like bulk density, tapped density, angle of repose, hausner's ratio and carr's index of powder blend was carried out which shows good flow properties of powder. The result shown in table 2

Table 2 Micromeritic properties of pre-compressional powder blend.

Batch No.	Angle of repose(Ɵ)	Bulk Density (gm/cc)	Tapped Density(gm/cc)	Carr's Index(%)	Hausner's Ratio
F1	27.98°±0.52	0.459±0.002	0.529±0.003	13.52±0.35	1.15±0.005
F2	25.35°±0.45	0.447±0.008	0.517±0.008	13.56±0.52	1.15±0.005
F3	26.24°±0.51	0.453±0.001	0.513±0.003	11.62±0.55	1.12±0.005
F4	27.73°±0.54	0.458±0.003	0.532±0.002	13.79±0.98	1.15±0.015
F5	29.40°±0.24	0.457±0.003	0.522±0.001	12.38±0.41	1.13±0.005
F6	27.16°±0.47	0.456±0.002	0.522±0.004	12.62±0.57	1.14±0.005
F7	25.94°±0.53	0.459±0.004	0.518±0.007	11.64±0.55	1.12±0.005
F8	27.31°±0.69	0.456±0.001	0.511±0.003	10.67±0.58	1.11±0.005
F9	28.94°±0.50	0.457±0.002	0.497±0.005	08.31±0.13	1.08±0.005
F10	29.67°±0.86	0.399±0.012	0.453±0.012	11.66±0.71	1.12±0.005
F11	29.10°±0.50	0.392±0.007	0.445±0.009	11.56±0.41	1.12±0.005
F12	26.09°±0.80	0.423±0.010	0.494±0.011	14.30±0.76	1.15±0.010

All values are expressed as mean ± SD, n=3

Sublingual tablets of Prochlorperazine maleate were prepared using various synthetic superdisintegrants like Indion 414 and kyron T-314 and natural superdisintegrants like Hibiscus rosa and Fenugreek in different concentrations by direct compression method. The formulation chart was shown in table.3

Table 3Composition of Prochlorperazine Maleate Sublingual Tablet.

Ingredients (mg)	Formulation code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Inclusion Complex equivalent to 5mg of drug	15	15	15	15	15	15	15	15	15	15	15	15
Indion 414	5	7.5	10									
Kyron T-314				5	7.5	10						
Hibiscus rosa							5	7.5	10			
Fenugreek										5	7.5	10
Mannitol	25	25	25	25	25	25	25	25	25	25	25	25
MCC	50	47.5	45	50	47.5	45	50	47.5	45	50	47.5	45
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2
Citric Acid	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Mg-stearate	1	1	1	1	1	1	1	1	1	1	1	1
Total weight	100											

The average weight of twenty tablets was calculated and the percentage deviations in weights were within the limits of ± 7.5% of the average weight. The hardness for all the formulations F1 to F12was ranged from 2.53±0.05kg/cm^2 to 3.00±0.1 kg/cm^2. The thickness for F1 to F12 formulations were ranged from 3.16±0.05mm to 3.46±0.05mm.The result was shown in table 4

Table 4 Post-compressional evaluation of different formulation of sublingual tablets of Prochlorperazine maleate

Batch no.	%Weight* variation	Hardness (kg/cm^2)	Thickness (mm)
F1	1.42	2.56±0.05	3.2±0.1
F2	1.12	2.66±0.20	3.33±0.05
F3	1.13	2.53±0.05	3.23±0.15
F4	1.13	2.73±0.15	3.4±0.1
F5	1.75	2.63±0.15	3.46±0.05
F6	1.53	2.6±0.10	3.36±0.15
F7	1.38	2.83±0.25	3.26±0.15
F8	1.60	2.56±0.05	3.23±0.05
F9	1.35	2.53±0.11	3.26±0.05
F10	1.70	3.00±0.10	3.16±0.05
F11	1.60	2.86±0.25	3.43±0.05
F12	1.45	2.83±0.25	3.26±0.05

All values are expressed as mean ± SD, n = 3, 20*

The percentage friability of all the formulations was found to be not more than 0.85±0.004, which was found to be well within the maximum 1 % limit. The result was shown in table 5The disintegration time for formulations F1 to F12 was ranged from 15.66±0.75 sec to 54.36±1.86 sec. The disintegration time of F3 containing 10 mg/tab of Indion 414 and F9 containing 10 mg/tab of hibiscus-rosa was minimum because of rapid uptake of water from the medium, swelling and burst effect. The result was shown in table.5 The Wetting time for formulations F1 to F12 was ranged from 25.26±1.45 sec to 64.16±2.25 sec. The Wetting time of F3 containing 10 mg/tab of Indion 414 and F9 containing 10 mg/tab of hibiscus-rosa was minimum because of wicking effect of disintegrating agent. The result was shown in table.5 The Water absorption ratio for formulations F1 to F12 was ranged from 40.96±0.42% to 73.23±0.67%.the Water absorption ratio of F3 containing 10 mg/tab of Indion 414 and F9 containing 10 mg/tab of hibiscus-rosa was maximum because of high uptake of water so higher the water absorption ratio. The result was shown in table 5

The percentage drug content of all the formulations was found to be between 98.12±0.27%to 100.42±0.42%, which were within the acceptable range. The result was shown in table.5

The percentage of drug released from F1, F2, F3 were found to be 98.16%, 97.1%, and 97.31% At 210 sec, 180 sec, 150 sec respectively. The percentage of drug released from F4, F5, F6 were found to be 97.67%, 97.22%, and 98.24% At 240 sec, 210 sec, 180 sec respectively. The rapid drug release was observed from the synthetic superdisintegrants in F3 is 97.31% from 150 sec. The result was shown in table.6

Table. 5 Post compressional Evaluation of different formulation of sublingual tablets of Prochlorperazine maleate.

Batch no.	%Friability*	Disintegration Time*(sec)	Wetting Time*(sec)	Water absorption ratio(%)	Drug Content(%)
F1	0.85±0.004	40.60±1.50	53.80±1.15	55.04±0.05	98.36±0.60
F2	0.65±0.11	26.20±1.55	35.13±1.20	66.69±0.65	98.22±0.40
F3	0.65±0.11	17.33±1.26	28.83±1.16	72.07±0.25	99.99±0.42
F4	0.49±0.10	52.26±2.05	63.50±1.35	43.10±0.92	98.55±0.91
F5	0.5±0.10	38.50±1.70	47.50±1.24	53.88±0.41	98.46±0.61
F6	0.32±0.05	27.43±0.75	36.60±1.50	62.94±0.18	99.66±0.71
F7	0.56±0.06	38.40±1.55	55.06±1.35	56.81±0.52	99.20±0.72
F8	0.52±0.14	26.23±1.10	37.13±1.45	66.14±0.45	98.22±0.40
F9	0.42±0.15	15.66±0.75	25.26±1.45	73.23±0.67	99.80±0.72
F10	0.56±0.11	54.36±1.86	64.16±2.25	40.96±0.42	99.19±0.52
F11	0.59±0.10	40.50±2.40	51.36±1.06	49.48±0.66	100.42±0.42
F12	0.46±0.15	30.53±1.30	38.43±1.16	57.94±0.28	98.20±0.40

All values are expressed as mean ± SD, n = 3, 10*

Table 6 *In-vitro* release of data formulations F1 to F6 (Synthetic superdisintegrants)

Time (sec)	Cumulative Drug Release (%)					
	F1	F2	F3	F4	F5	F6
15	28.11	32.34	40.82	23.87	26.18	30.03
30	39.44	43.69	52.99	35.56	37.88	41.37
45	48.51	53.94	63.29	43.07	46.56	52.38
60	57.63	62.72	72.49	52.55	55.67	63.06
90	66.04	71.92	81.36	61.69	64.45	72.65
120	74.87	80.38	89.89	70.89	73.27	80.75
150	82.97	88.53	97.31	77.82	82.91	91.97
180	90.36	97.1		84.02	91.07	98.24
210	98.16			90.63	97.72	
240				97.67		
270						

Table:7*In-vitro* release of data formulations F7 to F12 (Natural Superdisintegrants)

Time (sec)	Cumulative Drug Release (%)					
	F7	F8	F9	F10	F11	F12
15	27.34	30.80	41.20	15.78	20.02	26.57
30	38.27	41.37	51.83	24.34	30.14	37.11
45	46.95	50.84	64.05	34.49	39.94	47.71
60	55.68	59.98	73.64	42.00	48.63	56.83
90	65.62	71.07	82.52	52.62	57.37	64.85
120	74.06	78.02	90.67	60.23	66.54	73.29
150	80.24	86.92	99.25	68.64	74.99	81.00
180	89.15	96.63		74.41	82.71	89.53
210	97.33			81.74	90.47	98.48
240				89.50	97.89	
270				97.30		

The percentage of drug released from F7, F8, F9 were found to be 97.33%, 96.63%, and 99.25% At 210 sec, 180 sec, 150 sec respectively. The percentage of drug released from F10, F11, F12 were found to be 97.30%, 97.89%, and 98.48% At 270 sec, 240 sec, 210 sec respectively, The rapid drug release was observed from the Natural superdisintegrants in F9 is 99.25 from 150 sec. The result was shown in table.7

The rapid drug release was observed in F3 and F9, which releases 97.31 % and 99.25 % respectively at the end of 150 sec. The rapid drug dissolution might be due to easy breakdown of particles due to presence of disintegrants.

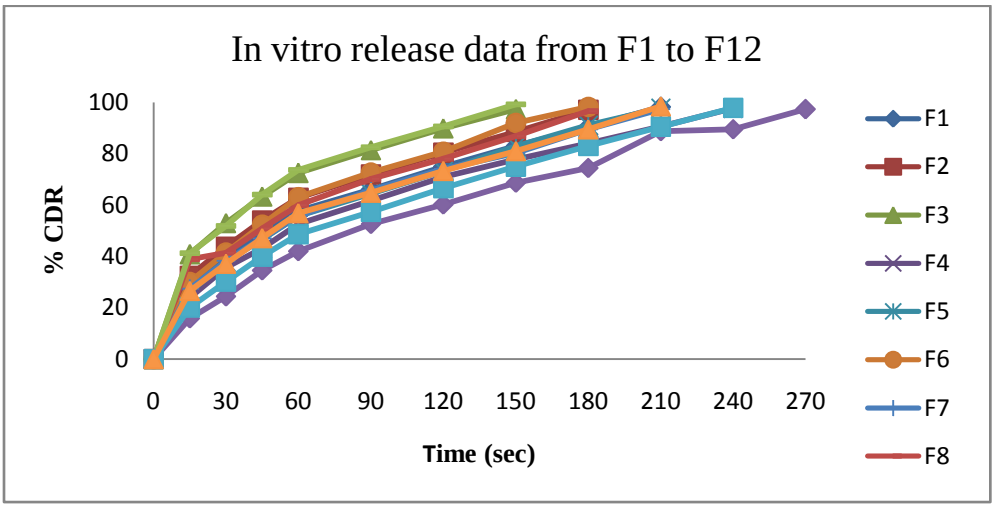

Figure 5 Comparison of *In Vitro* release data of Formulation F1 to F12

CONCLUSION

In the present work, the effects of various superdisintegrants on Prochlorperazine maleate sublingual tablet were studied. The post Compressional parameters of prochlorperazine maleate sublingual tablets such as hardness, friability, wetting and disintegration time, water absorption ratio and *in-vitro* dissolution profile results complies with the reported literature limits. Overall, formulation F3 (10 mg of Indion 414) and F9 (10 mg of Hibiscus-rosa) based on disintegration time, wetting time and drug release were found to be an excellent formulations. Hence it was found that there was no significant difference between F3 and F9, which shows that natural superdisintegrant (10 mg of Hibiscus rosa) is as good as synthetic super disintegrants (10 mg of Indion 414). Hence it proves that synthetic disintegrant can be replaced by natural disintegrant due to easy availability, compatibility.

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