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Formulation and Evaluation of Sustained Release Mucoadhesive Tablet of Cinnarizine HCL.

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Abstract: The present study was aimed to formulate and evaluate sustained release mucoadhesive tablets of Cinnarizine HCL by wet granulation method. Cinnarizine is used as an anti-histaminic and anti- emetic agents with half-life 3-4 hrs. In this study, excipients like Carbopol 934, Xanthan gum were incorporated in a 13 different concentrations (F1-F13) along with other excipients (DCP, Talc and Magnesium sterate) to formulate sustained release mucoadhesive tablet by wet granulation method. Then all the 13 formulations were evaluated for uniformity of weight, hardness, thickness, friability test, swelling index, drug content, dissolution studies and stability studies. The dissolution profile of batch F3 were observed to be better than other formulations. In batch F3, Cinnarizine was formulated as a sustained release mucoadhesive tablet by using Carbopol 934 (130 mg), Xanthan gum(70 mg). Batch F3 showed a better in-vitro drug release profile, swelling index(190%), drug content(99.99%), ex-vivo residence time (11hrs) and mucoadhesive strength (35g) relieved the best batch among all formulations. Thus, it can be concluded that the sustained release mucoadhesive tablet of cinnarizine using the appropriate polymers in right amount may enhance the activity of the drug by prolonging the gastric residence time, improved bioavailability and increase therapeutic effect.

Introduction:-

Mucoadhesive delivery system offer several advantages over other controlled release systems by virtue of prolongation of residence time of drug, its targeting, and localization of the dosage form at a specific site. These advantages include bypass of first pass metabolism of the drug and hence more concentration of the drug is available for absorption. Mucoadhesion occurs between two surfaces, one of which is a mucous membrane and another is drug delivery system. These mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting in a high drug influx through the absorbing tissue. Mucoadhesive formulations use polymers as the adhesive component. Mucoadhesive drug delivery systems are available in the form of tablets, films, patches and gels for oral, buccal, nasal, ocular, vaginal, rectal and topical routes for both systemic and local effects (Muraleedhara *et al*., 2013). Oral administration is the major route for drug delivery. Oral controlled release systems are used for controlled action of active ingredients to the targeted site. But oral controlled release systems have many problems such as first pass hepatic metabolism, enzyme degradation, swallowing problem etc. So, as compared to oral controlled release systems, mucoadhesive delivery system have several advantages like prolongation of residence time, drug targeting, intimate contact between dosage form and the absorptive mucosa. In addition, mucoadhesive dosage forms have been used to target local disorders at

the mucosal surface to reduce dose and to minimize the side effects. Mucoadhesive formulations use polymers as the adhesive component. These polymers as water soluble. When polymers are used in a dry form, they attract water from the mucosal surface and leads to a strong interaction which increases the retention time over the mucosal surfaces. Prolonged contact time of a drug with a body tissue through the use of a bio adhesive polymer can significantly improve the performance of many drugs (Saraswati *et al*., 2013).

Methods and materials

Cinnarizine was obtained as gift sample from Hochest Biotech India. Different polymers and excipients like Carbopol 934P, Xanthan Gum, Magnesium stearate, n-propyl alcohol, Talcum powder were purchased from Ramson pharmaceutical industries. All other ingredients used were of laboratory grade.

Preformulation studies:

The parameters like melting point, IR Spectra, angle of repose, bulk density, tapped density, Hausner's ratio were determined as the part of preformulation studies.

Drug-excipients compatibility studies:

Compatibility studies were carried out to know the possible interactions between Cinnarizine HCL and excipients used in the formulation. Physical mixture of drug and excipients were prepared to study the compatibility using the Infra-Red spectrophotometer.

Preparation of Cinnarizine Mucoadhesive tablet:

Tablets containing the 50 mg of Cinnarizine HCL were prepared by the conventional non-aqueous wet granulation method employing Carbopol 934P, Xanthan gum, dicalcium phosphate, talc and magnesium sterate. Batches of 100 tablets were prepared in each case. In the previously prepared granules talc and magnesium sterate were added and mixed well. Weighed the granules individually according to the tablet weight. Then granules were compressed into 350 mg tablets of hardness 6-7 Kg/cm2 on a tablet compression machine using 12mm punch. Thirteen different batches were prepared using the same procedure (Dawange *et al*., 2015).

Table1: Formulation batches of Cinnarizine HCL Mucoadhesive tablet:

S.No.	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
1	Cinnarizine HCL	50	50	50	50	50	50	50	50	50	50	50	50	50
2	Carbopol 934	150	140	130	120	110	100	90	80	70	60	50	-	200
3	Xanthan gum	50	60	70	80	90	100	110	120	130	140	150	200	-
4	DCP	90	90	90	90	90	90	90	90	90	90	90	90	90
5	Talc	4	4	4	4	4	4	4	4	4	4	4	4	4
6	Magnesium sterate	6	6	6	6	6	6	6	6	6	6	6	6	6

Evaluation of mucoadhesive tablet

1. **Weight Variation test**: 20 tablets were taken and each tablet was weighed individually using the electronic balance. The average weight of the tablet was calculated and considered as the standard weight of the individual tablet. Then all the tablets were individually weighed and the percentage weight variation was calculated from the following formula to determine whether the individual weight is within the range or not. Deviation of weight variation is given in the table 2.

   Table2: %Deviation for Weight variation

Average weight	Percent difference
130mg or less	±10
More than 130mg	±7.5
324 mg or above	±5

2. **Hardness test:** To evaluate the tablet hardness, Monsanto hardness tester was used. The tester consists of a barrel containing a compressible spring held between two plungers. The plunger was placed in Contact with the tablet and zero reading was taken. The upper plunger was then forced against a spring by turning a threaded bolt until the tablet fractures. The spring forced against a spring by turning a threaded bolt until the tablet fractures. As the spring was compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture was recorded and then Zero force reading was deducted from it (Lachman *et al*.,2015).
3. **Thickness test:** Tablet thickness was determined using the micrometre screw gauge. Thickness of tablet is important for uniformity of tablet size.
4. **Friability test:** Roche friabilator was used to check the friability of the tablet. This device, subjects a number of tablets to the combined effects of abrasion and shock by utilizing plastic chamber that revolves at 25 rpm, dropping of tablets a distance of six inches with each revolution. A per weighed tablets sample was placed in the friabilator, which was then operated for 100 revolutions. The tablets were then dusted and reweighed (Lachman *et al.*, 2015).
5. **Drug content**: Weighed and powdered the 20 tablets. Shake a quantity of the powdered tablets containing about 25mg of Cinnarizine Hydrochloride with methanol, dilute 50.0ml with the same solvent and filter. Dilute 5ml of this solution to 50ml with methanol and measure the absorbance of the resulting solution at the maximum at about 253nm.
6. **Swelling index:** Swelling of tablet excipients involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particle through pores and blind to large molecule, breaking the hydrogen bond and resulting in the swelling of the particle.
7. **In-vitro drug release study**: In-vitro dissolution studies for all prepared tablets were carried out using USP Paddle method. Placed the 900ml pf the dissolution medium (0.1 N HCL) free from dissolved air, into the vessel of the apparatus. Assembled the apparatus and warmed the dissolution medium to 36.5 □to 37 □5. Placed the tablet in

the vessel. Operated the apparatus immediately at the speed of 50 rpm. After the 1,2,3,4,5,6,7,8,9,10,11 and 12 hours samples were withdrawn from a zone midway between the surface of the dissolution medium and the top of the rotating paddle , not less than 10mm from the wall of the vessels . An equal volume of pre -warmed (37 □C) fresh medium was replaced into dissolution medium after each sampling to maintain the constant volume throughout the test. Filtered the sample solution promptly through a membrane filter disc with an average pore diameter not greater than 1.0 micrometre. Discard the first few ml of the filtrate and noted absorbance spectrophotometrically at 253 nm. Then the cumulative percentage of drug release was calculated and represents graphically (I.P., 2020).

8. **Mucoadhesive strength test:**

Mucoadhesive strength of the tablet was measured on the modified physical balance. The apparatus consists of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A Teflon block of 3.8cm diameter and 2cm height was fabricated with an upward portion of 2cm height and 1.5 cm diameter on one side. This was kept in beaker filled with buffer media 0.1N HCL pH1.2, which was then placed below right side of the balance. Goat stomach mucosa was used as model membrane and buffer media 0.1N HCL pH1.2 was used as moistening fluid. The goat stomach was kept in Krebs buffer during transportation. The underlying mucous membrane was separated using surgical blade and wash thoroughly with buffer media 0.1 N HCL. It was then tied over the protrusion in Teflon block using a thread. The block was then kept in glass beaker. The beaker was filled with phosphate buffer media 0.1 N HCL. Upto the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments. The one side of tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat stomach mucosa and mucoadhesive tablet was established (Sandhya *et al*., 2014). A preload of 10 mg was placed on the slide for 5 min to established adhesion bonding between mucoadhesive tablet and goat stomach mucosa. The preload time were kept constant for all formulations. After completion of preload time, preload was removed from the glass slide and then added weight of 5g in left side arm. Then, the weights were increased on the right pan until tablet just separated from mucosa membrane. The addition of weights was stopped when mucoadhesive tablet was detached from goat stomach mucosa was noted as mucoadhesive strength in grams. From the mucoadhesive strength following parameter was calculated.

9. **Stability study:**

Stability studies were conducted only on optimized formulation. The formulation were packed with aluminium foil and subjected to stability studies at different temperature and humidity condition as per ICH guidelines viz . room temperature (28 □C) AND 40 □C/75% RH. Samples were withdrawn at time intervals of 30,60 and 90 days. These were evaluated for possible weight variation, hardness and % drug content and in-vitro drug release. In-vitro release was studied by spectrophotometrically method (Panigrahy et al., 2011).

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RESULTS AND DISCUSSION

The prepared mucoadhesive tablet were evaluated for various physical properties. The physical attributes of the mucoadhesive tablets were found to be satisfactory . Typical tablet defects were not observed . Preformulation studies were done as mentioned in methods. The melting point was observed to be 119 □C which shows that the cinnarizine HCL was pure. Formulation of mucoadhesive tablets were as per wet granulation method. The prepared tablets were then evaluated for parameters such as weight variation, Hardness, friability and thickness, swelling index and mucoadhesive strength test.

To check the purity of drug, the spectra shows characteristic peaks of cinnarizine similar to the standard spectra given in the instrumentation analysis. The IR Spectra is given in the figure 1.

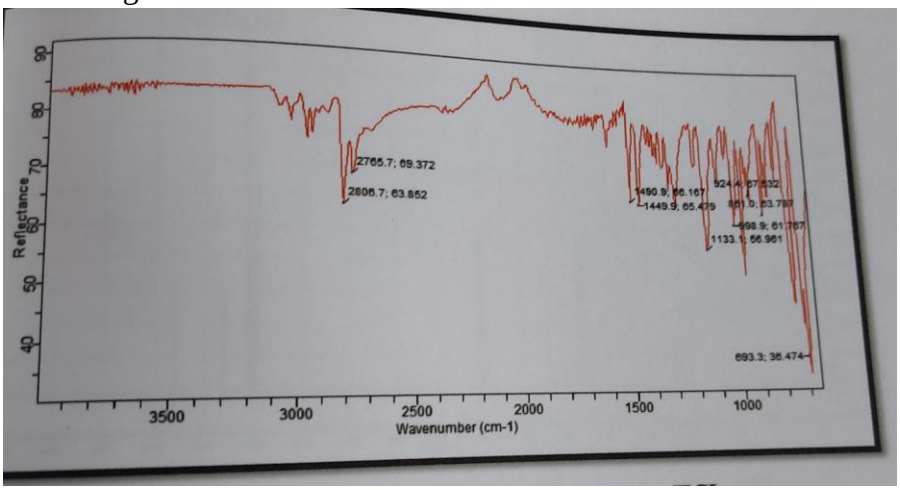


Figure 1: FTIR Spectrum of drug Cinnarizine HCL.

To check the interaction between drug and excipients, used in the formulations, IR studies were performed. In IR studies were performed. In IR study, it was found that all the prominent peaks which were present in individual graphs of cinnarizine were also present in IR of physical mixture between drug and excipients. Thus, we can say there was no significant interaction between drug and Excipients. The drug and excipients spectrum are given in figure 2.

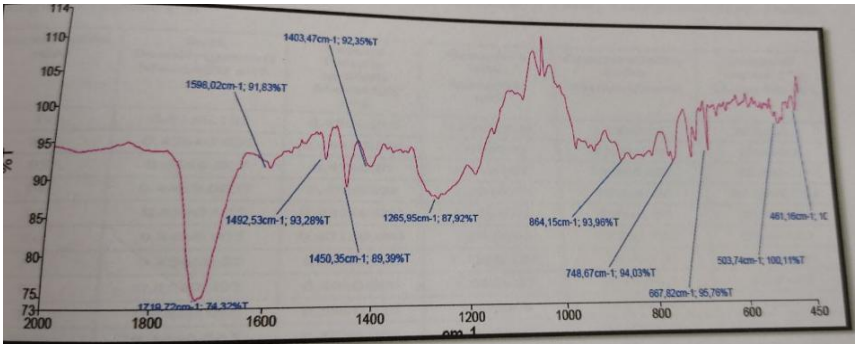


Figure2: FTIR Spectrum of Cinnarizine HCL+ Carbopol 934P + Xanthan gum

The powder mixtures prepared for compression of mucoadhesive tablets were evaluated for their flow properties . Angle of Repose was in the range of 25.7 □ to 32.7 □. Tapped density was found to be in the range of0.47-0.50gm/ml. Carr's index was in the range of 8.45 to 15.01% and Hausner's Ratio was in the range of 0.13-1.17 for the powder mixture of different formulation. All the result indicated that, the powder blends possess good flowability and compressibility properties. (Table 3)

Table3: Bulk Density, Tapped Density, Hausner's ratio, Compressibility index and Angle of Repose of mucoadhesive tablet.

Formulation code	Bulk Density(gm/ml)	Tapped Density(gm/ml)	Hausner's ratio	Compressibility Index	Angle of Repose (□)
F1	0.41±0.102	0.49±0.013	1.07±0.005	11.8±0.36	30.12±1.1
F2	0.426±0.001	0.49±0.003	1.09±0.01	11.6±0.55	29.6±0.8
F3	0.43±0.007	0.48±0.01	1.11±0.01	11.5±0.091	32.24±1.7
F4	0.44±0.003	0.47±0.008	1.13±0.02	13.5±0.56	30.24±0.72
F5	0.45±0.005	0.49±0.003	1.17±0.03	9.81±1.05	25.7±0.85
F6	0.44±0.005	0.47±0.004	1.09±0.03	11.2±1.011	29.6±1.01
F7	0.424±0.02	0.49±0.003	1.17±0.264	14.9±1.3	32.7±1.96
F8	0.45±0.007	0.49±0.006	1.08±0.03	15.01±1.5	29.3±1.6
F9	0.44±0.015	0.50±0.015	1.13±0.4	15.01±0.79	32.0±4.53
F10	0.44±0.003	0.47±0.001	1.06±0.49	13.5±0.20	32.36±1.21
F11	0.43±0.003	0.49±0.002	1.17±0.02	8.45±0.7	32.36±1.21
F12	0.421±0.001	0.49±0.003	1.16±0.01	9.72±0.55	31.73±0.8
F13	0.43±0.003	0.50±0.002	1.13±0.02	10.9±0.7	29.5±1.21

The tablets of all formulations were tested by various studies including weight variation (ranging from 1.8-5.5%), Hardness (ranging from 6.2-6.7 mm), Thickness (4.2-4.9mm) and friability (ranging from 0.16-0.73%). All the 13 formulations passed the evaluation as per the I.P Limits. The evaluated properties showed good enough results for the further studies.

Table4: Weight Variation, hardness, thickness, diameter and friability of mucoadhesive tablet.

Formulation code	Weight variation(%)	Hardness (Kg/cm3)	Thickness(mm)	Diameter (mm)	Friability
F1	2.7±0.54	6.6±0.05	4.8±0.05	11.2±0.56	0.31±0.009
F2	3.4±0.22	6.4±0.17	4.8±0.57	11.2±0.76	0.35±0.028
F3	1.8±0.23	6.5±0.20	4.7±0.65	11.2±0.51	0.48±0.007

F4	2.0±0.21	6.7±0.26	4.9±0.76	11.2±0.42	0.34±0.019
F5	3.6±0.43	6.3±0.26	4.9±0.160	11.2±0.62	0.20±0.013
F6	3.0±0.21	6.5±0.17	4.8±0.817	11.2±0.74	0.16±0.08
F7	5.5±0.22	6.6±0.20	4.2±0.077	11.2±0.50	0.66±0.12
F8	2.6±0.53	6.4±0.161	4.2±0.817	11.2±0.65	0.39±0.045
F9	4.0±0.18	6.7±0.24	4.8±0.50	11.2±0.86	0.73±0.060
F10	3.2±0.21	6.6±0.05	4.2±0.06	11.2±0.70	0.40±0.015
F11	3.3±0.19	6.2±0.36	4.7±0.52	11.2±0.71	0.62±0.007
F12	2.6±0.54	6.5±0.15	4.8±0.57	11.2±0.60	0.16±0.084
F13	3.5±0.28	6.6±0.20	4.9±0.09	11.2±0.54	0.39±0.119

In-vitro release of the mucoadhesive tablet was formulated by making 13 batches(F1-F13). Out of 13 batches, only 7 batches were passed F2,F3,F5.F7.F8 and F12, F13. These 7 batches revealed better sustain release within 12 hrs between the range 96-99%. Various release kinetics model such as Zero order, first order, Higuchi model and koresmeyer-peppas release model were studies.

Table 5: Correlation coefficient of Kinetic Modelling

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas
F1	0.990	0.604	0.939	0.733
F2	0.943	0.496	0.963	0.571
F3	0.969	0.625	0.957	0.732
F4	0.968	0.864	0.841	0.985
F5	0.978	0.748	0.925	0.926
F6	0.990	0.648	0.923	0.720
F7	0.869	0.575	0.924	0.707
F8	0.942	0.622	0.953	0.823
F9	0.971	0.641	0.925	0.754
F10	0.970	0.686	0.940	0.795
F11	0.988	0.690	0.930	0.776
F12	0.985	0.792	0.881	0.908
F13	0.979	0.769	0.873	0.935

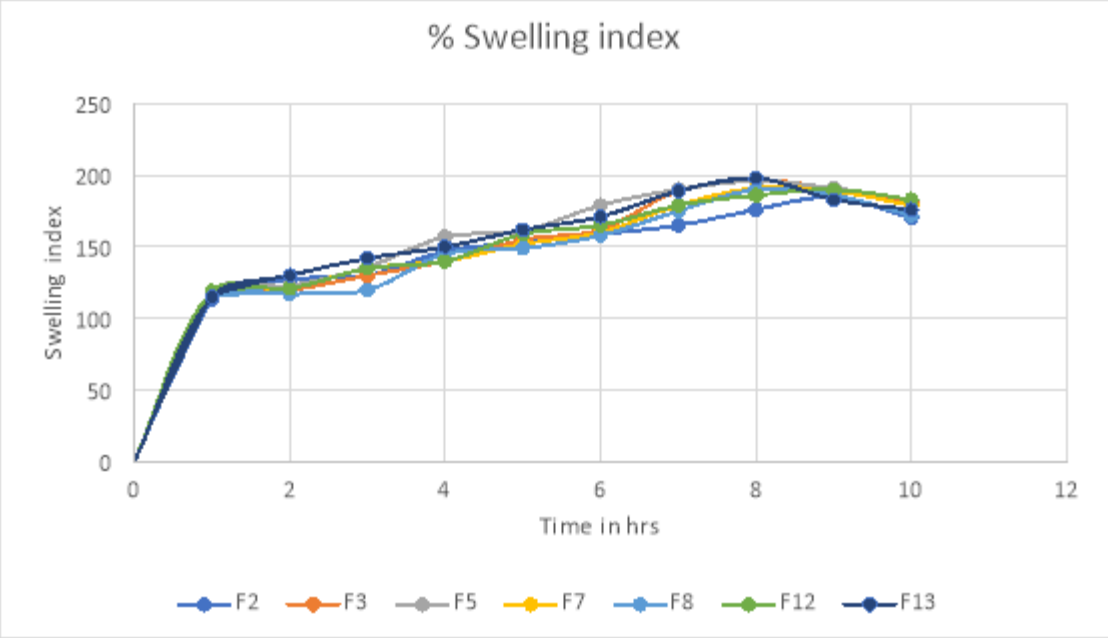
Table 6: Physical evaluation parameters of for formulation F3 during stability study.

Sampling time Interval (Months)	Appearance	% Weight Variation	Hardness	% CDR	Assay
Initial	White	1.8±0.31	6.5±0.26	99.98±0.32	99.7±0.13
1 Month	White	2.0±0.23	6.3±0.31	99.12±0.03	99.6±0.55
2 Month	White	1.9±0.44	6.1±29	98.92±0.11	99.5±0.45
3 Month	White	2.5±0.04	6.4±0.20	99.94±0.11	99.2±0.01

Table 7: Swelling Index

Time in Hrs	Formulation Code						
	F2	F3	F5	F7	F8	F12	F13
0	0	0	0	0	0	0	0
1	113	118	119	118	115	119	155
2	127	120	123	121	117	121	130
3	130	130	136	135	120	135	142
4	147	140	157	140	145	140	150
5	153	155	161	152	149	159	162
6	159	162	179	160	158	165	171
7	165	189	190	179	175	179	189
8	176	197	196	191	190	186	198
9	185	190	191	189	186	190	183
10	170	181	183	179	172	183	176

The swelling behaviour of a bio adhesion system is an important property for uniform and sustained release of a drug and bio adhesion. The swelling behaviour depends upon nature of polymers, concentration of polymer and pH of the medium. Percentage swelling index of all the formulations F2, F3, F5, F7, F8, F12 and F13 was found to be in the range 113% and 183%. F3 batch was passed because this batch having good swelling properties in comparison to others formulations within 10 hrs.



Conclusion: The present study performed on formulation and evaluation of sustained release mucoadhesive tablet of Cinnarizine HCL. Mucoadhesive Tablet were prepared by various polymers alone and in combination (Carbopol 934P, Xanthan Gum). The prepared tablets of selected batches F2, F3, F5, F7, F8, F12 and F13 were in the acceptable range of weight variation, friability, thickness, hardness and drug content as per pharmacopoeias specification. The surface pH of prepared tablets of selected batches were in the range of neutral batches, suggested that prepared tablets could be used without risk of mucosal irritation. As per in-vitro drug release selected batches showing 92% to 99.8% release in 12 hours. The prepared tablets of selected batches showed good swelling, up to 10hrs. in 0.1N HCL. Maintaining the integrity of formulation which is required for bio adhesion, ex-vivo residence time (Average detachment time of mucoadhesive tablet) was 5 hrs 18 min to 11 hrsand mucoadhesive strength 25 to 47 gm. Suggest the selected formulations remain intact with gastric mucosa for all time to release the drug in controlled manner. Batch F3 showed better in-vitro drug release profile (%), swelling index (190%), drug content (99.97%), surface pH(7.0), ex-vivo residence time(11hrs.) and mucoadhesive strength (35.5g) from all selected batches, relived the best batch among all formulations. Hence mucoadhesive tablet of Cinnarizine HCL prepared with selected polymeric blend concluded the improved bioavailability and increase therapeutic effect.

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