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Formulation and Evaluation of Fast Dissolving Films of Dextromithorphan Hydrobromide and Chlorpheniramine Maleate

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Abstract : The main objective of the study was to formulate and evaluate fast dissolving film containing Chlorpheniramine maleate and Dextromethorphan hydrobromide. Fast dissolving films were prepared by solvent casting method without any organic solvents. Compatibility of Chlorpheniramine maleate and Dextromethorphan hydrobromide combination and both the drugs with polymer was confirmed by FTIR study and DSC study. Prepared films were analyzed for various parameters like weight variation, thickness, folding endurance, drug content, tensile strength, % elongation, disintegration time and % Drug release. All the formulations have good folding endurance. Also no any major difference in weight variation as well as thickness. Surface pH was found near to 7 for all formulations. Tensile strength and % Elongation found satisfactory in all batches. From all the formulations, formulation F17 which contain 200 mg of HPMC 3 cps film forming polymer was optimized because it gives maximum drug release in 10 min which was maximum drug release in less time in all formulations. Also F17 have disintegration time 26 sec and have good mechanical properties. Drug content also found within limit. So F17 was optimized batch.
Key Words : Chlorpheniramine maleate, Dextromethorphan hydrobromide, fast dissolving Film.

Introduction:

Dextromethorphan Hydro bromide and Chlorpheniramine Meleate are belonging to class of antitussives and antihistamine respectively. Therefore, development of combination treatment of these drugs for the cough suppressant and can have potential action over the single drug treatment for geriatric and pediatric patients. Apart from tablets and syrups type dosage form, mouth dissolving films are acceptable approach for quicker action and uniform dose for geriatric and pediatric patients.

Quick onset of action can easily achieved because the film can rapidly dissolved in mouth within seconds compared to tablets. Therefore, patient acceptance might be improved due to elegant appearance and mouth pleasant taste of film. Also, distribution of drug into film is uniform in every strip that can help for uniformity of dose over the syrup.

This masked active ingredient is than swallowed by the patient's saliva along with the soluble and insoluble excipients. The target population for these new fast dissolving dosage forms have generally been pediatric, geriatric and bedridden or developmentally disable patients. Pharmaceutical marketing is another reason for the increase in available fast dissolving/disintegrating products. The major advantage of FDT is that

it combines the advantage of both liquid and conventional tablet formulation, while offering advantages over both traditional dosage forms.[1, 2]

Experimental Work

Preformulation Study

Drug-Excipients compatibility

DSC study: The DSC thermograms of pure drug, other excipients and optimized film were recorded. DSC study was performed for Drug and physical mixture of all ingredients of optimized film.

FTIR Study: The FTIR of pure drug and physical mixture of formulation ingredients of optimized batch was measured using Fourier transform infrared spectrophotometer (Model FTIR-8400S, Shimadzu, Japan). The amount of each formulation ingredient in the physical mixture was same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400 cm^{-1}.

Preparation of Standard Calibration Curve

Preparation of stock solution: Stock solution was prepared by dissolving 10 mg ofboth the drugs separately into 50 ml of methanol. (200 µg/ml)

Scanning: From the stock solution 50µg/ml was prepared in methanol and UV scanwas taken between 200 to 400 nm. The Zcp values (the λmax value of one drug will become Zcp value of another drug in first derivative UV spectro photometry and for further study absorption should be taken on that determined Zcp values) were found to be Dextromethorphan hydro bromide has absorbance maxima at 222 nm and Chlorpheniramine maleate has absorbance maxima at 264 nm in methanol and were used for the further analytical studies.

Calibration curve of Chlorpheniramine maleate in methanol: From the standard stock solution (200 µg/ml), appropriate aliquot were transferred to series of 10 ml volumetric flasks and made up to 10 ml with methanol so as to get concentration of 05,10,20,30,40 and 50 µg/ml. the absorbance of solution were measured at 264 nm. This procedure was performed in triplicate to validate calibration curve. A calibration graph was plotted.

Calibration curve of Dextromethorphan hydro bromide in methanol: From the standard stock solution (200 µg/ml), appropriate aliquot were transferred to series of 10 ml volumetric flasks and made up to 10 ml with methanol so as to get concentration of 20,30,40,50,60,70,80 and 90 µg/ml. the absorbance of solution were measured at 222 nm. This procedure was performed in triplicate to validate calibration curve. A calibration graph was plotted.

Peparation of Fast Dissolving Film of Chlorpheniramine Maleate and Dextromethorphan Combination:

The present favored developed procedure for making this film is solvent casting without any organic solvents. Polymer (HPMC E5 LV, HPMC E15 LV, and PVA) was heated into 5 ml of water to dissolve. Plasticizer (PEG 400) and super disintegrants (Cross Carmellose sodium) were added into polymeric solution than the solution is kept aside for two hr to remove air entrapment. Drugs (Chlorpheniramine maleate and Dextromethorphan) and sweeteners (Aspartame, Neotame,) were dissolved into in to 3 ml of water. Drugs solutions were added into polymeric solution and stir the solution for an hr to get uniform viscous solution. The form bubble free viscous solution was casted into casting plate having diameter of 8 cm. The casting plate than kept at room temperature for 12 hr for drying of the film. Dried film was then cut into 2 cm^2 size and shape for the intended application.

Formulation preparation of film

- ✓ Amount of 3ml of plastisizer sufficient to prepare a good film, so now onwards 3 ml PEG 400 used.
- ✓ KyronT-104 resin in amount of 1:0.5, 1:0.75, 1:1 and 1:1.25 ratio uses in comparision of Drug for taste masking.

Evaluation Parameters of Fast Dissolving Film:

Weight variation of film: Two square inch film was cut at five different places in the cast film. The weight of each film strip was taken and the weight variation was calculated. [3]

Thickness of film: The thickness of film was performed by screw gauge at different position of the film and the average thickness was calculated.[38]

Folding endurance: The folding endurance is expressed as the number of folds (number of times of film is folded at the same plain) required breaking the specimen or developing visible cracks. [5, 6, 7]

Disintegration time: Disintegration time was performed using disintegration test apparatus. Two square inch film was placed in the basket, raised and lowered it in such a manner that the complete up and down movement at a rate equivalent to thirty times a minute.[6, 7, 8]

Mouth dissolving time: The mouth dissolving time was determined by placing the film manually into a petridish containing 10 ml of 6.8 pH phosphate buffer. Time required by the film to dissolve was noted.[9, 10]

% Drug content: The films were evaluated for % drug content. Films of size two square inches was cut, placed in 100 ml of volumetric flask and dissolved in phosphate buffer 6.8, volume was made up to 100 ml. One ml of the solution from the 100ml volumetric flask was taken into 10 ml of volumetric flask and made the volume up to 10 ml with methanol. The absorbance of the solution was measures at 264 nm and 222 nm for Chlorpheniramine maleate and Dextromethorphan respectively.[10]

Surface pH: The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible.

In-vitro dissolution study: Dissolution study was carried out using USP type I (basket apparatus) with 300 ml of 6.8 pH phosphate buffer as dissolution medium maintained at 37 ± 0.5^0C. Medium was stirred at 50 rpm for periods of 30 min. Samples were withdrawn at 2, 5, 10, 15, 20 and 30 min interval, replacing the same amount with the fresh medium. From withdrawn samples one ml of solution was taken and was diluted up to 10 ml with methanol and analyzed at 264 nm and 222 wavelengths for Chlorpheniramine maleate and Dextromethorphan respectively.[10, 11].

TensileStrength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. The tensile strength (TS) can be calculated by dividing the maximum load in Newton by the original cross-sectional area of the specimen and it is expressed in force per unit area (N/mm^2) or MPa.

Stability study:

It is vital for formulation development person to develop a stable product from formulation as well as regulatory point of view. The regulatory agencies around the globe have rhetoric guidelines of product stability studies. The stability study is performed to check physical and chemical integrity of the formulation**.**

The selected batches were subjected for stability study. All the FDF were suitably packed in aluminum foil. The FDF to be stored at 40 ^{o}C / 75 % RH condition. At the end of 1 month, the sealed FDF were opened and evaluated for different parameters.

Results and Discussion

Preformulation Study:

Characterization of drugs

- **Chlorpheniramine Maleate**

- ***Description:-*** White, odorless, crystalline powder
- ***Solubility: -*** Freely soluble in water; soluble in methanol
- ***Odour:-*** Odorless

- **Dextromethorphan Hydrobromide**

- ***Description:-*** white, crystalline powder
- ***Solubility:-*** soluble in water and methanol
- ***Odour:-*** Odorless

Both drugs were found soluble in water so it is useful to prepare film by taking water as a solvent in solvent casting method. Also both drug found odour less.

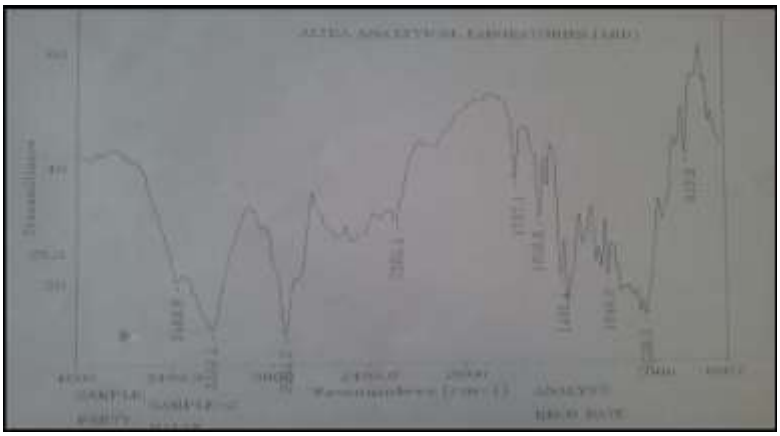
Drug-Excipients compatibility study

FTIR spectroscopy

The individual drugs and both the combination of drugs and drugs with polymer were separately scanned. All the spectra were compared for confirmation of common peaks. Chlorpheniramine Maleate and Dextromethorphan and combination with polymer showed no significant variation in intensity and position peaks, suggesting that drugs and excipients were compatible.

Hence, it can be concluded that both the drugs (Chlorpheniramine Maleate and Dextromethorphan) is in Free State. The characteristic peaks of the pure drug Chlorpheniramine Maleate as N-H stretch (2626.87 cm-1), aromatic C-H stretch (3028.1 cm-1), C=O stretch (1739.67 cm-1), aromatic C-N stretch (1352.66 cm-1) and out. The characteristic peaks of pure drug Dextromethorphan as N-H stretch (3285.95 cm-1), aromatic C-H stretch (2515.88 cm-1).

Both the drugs with combination and with polymer shown same characteristic peaks. So, it was shown the presence of the drug in the formulations and confirms the compatibility of drug with the polymer.



DSC Study

The thermograms of Dextromethorphan hydrobromide, Chlorpheniramine Maleate and Film without resin exhibited sharp endothermic peak at 123°C, 135°C and 145°C respectively with no apparent decomposition up to a temperature of 300°C.

Kyron T-104 exhibited broad endothermic asymmetrical peak between 50–150°C with melting point at 61°C that was retained in Final film indicating that the drugs were not in their native forms in resinate. However the peak of Final film spectra was less asymmetrical than melting peak of Kyron T114 and the melting point shifted to 78 °C confirming the chemical interaction between drugs and resin.

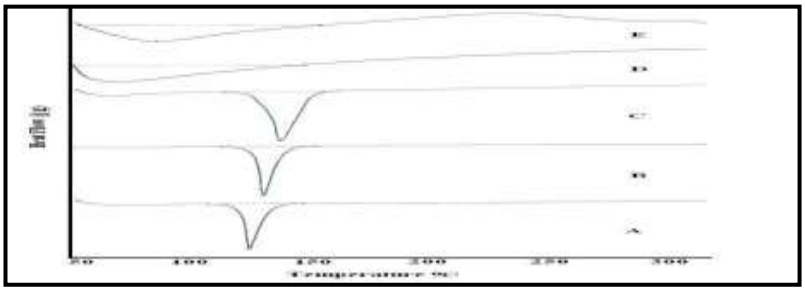


Figure 6.3:- DSC thermograms of;

a. Dextromethorphan Hydrobromide
b. Chlorpheniramine Maleate
c. Film without resin
d. Kyron T-104
e. Final Formulation

Evaluation of Fast Dissolving Film:

Prepared fast dissolving films was evaluated for different parameters and results were given in below sections.

Here we can see that (table 6.1) the amount of PEG 400 in different amount gives different results on film flexibility.

- ✓ 2 ml amount gives brittle film.
- ✓ 3 ml of plastisizer give goods flexibility to film.
- ✓ 5 ml amount was little bit higher for film and give stickiness to film during casting.
- ✓ Based on above results it concluded that 1:1 ratio of drug to resin was good enough to release a drug in early time as well as Taste masking also done.

Evaluation of Mouth dissolving films formulation F8-F19

- ✓ F8-F19 Formulation is taken for evaluation for various parameters which were discussedpreviously. Results are recorded in following table 6.3.
- ✓ Weight variation and thickness found uniform in all formulation, no any major deviation found. (table 6.3.1)
- ✓ Folding endurance found more than 250 for all formulation. we can see that the film which contains higher amount of polymer have a good folding endurance.
- ✓ Surface pH of formulation F8-F19 was found between 6.5 - 7.1.
- ✓ All formulation has good mechanical properties because folding endurance was more than 250 for all. Also tensile strength found 1.8-2.4 N/mm^2. More amount of polymer in films gives more tensile strength and same for % Elongation.

Evaluation of F8-F19 for In-vitrodisintegration time

In-vitro disintegration time of formulation F8-F19 given in table 6.3.6. It indicates that low amount of polymer in films gives less time for disintegration. Those batches which contain higher amount of polymer have a disintegration time more than 1 min. F16 batch have less time 26 sec to disintegrate.

Evaluation of F8-F19 for *In-vitro* drug release of Dextromethorphan Hydrobromide

- ✓ From the drug release data of formulation F8-F19 given in above table 6.3.7, it concluded that in F8 amount of polymer 300 mg is high so drug release not seen from the film or slow drug release seen.
- ✓ Amount of polymer decrease in F12-F19 give better drug release than the previous.
- ✓ Again in F16-F19 amount of polymer decrease to achieve fast drug release in 5-10 min.
- ✓ HPMC 3 cps gives drug release in 10 min which was maximum % drug release in all formulations.
- ✓ Other polymers are not give proper drug release as per our desired profile.
- ✓ So based on that F17 which contain 200 mg of HPMC 3 cps optimized.

STABILITY STUDY

- ✓ Stability Study of Optimized formulation F17 performed for 1 month.
- ✓ Formulation found stable during stability at 40 ^{0}C / 75 % RH.
- ✓ Results of stability study given in below table 6.4.

Table 5.1: Calibration curve of Chlorpheniramine maleate in methanol

Sr. No	Concentration (µg/ml)	Mean Absorption ± SD
1	0	0
2	10	0.029 ± 0.002
3	20	0.048 ± 0.003
4	30	0.081 ± 0.001
5	40	0.108 ± 0.004
6	50	0.120 ± 0.003
7	60	0.149 ± 0.002

Table 5.2: Calibration curve of Dextromethorphan hydrobromide in methanol

Sr. No	Concentration (µg/ml)	Mean Absorption ± SD
1	0	0
2	20	0.007 ± 0.0005
2	30	0.013 ± 0.0010
3	40	0.019 ± 0.0005
4	50	0.025 ± 0.0035
5	60	0.032 ± 0.0011
6	70	0.039 ± 0.0005
7	80	0.046 ± 0.0005
8	90	0.055 ± 0.0011

Table 5.3: Screening of amount of for Plastisizer in fast dissolving film

Ingredients (mg)	F1	F2	F3
Chlorpheniramine maleate	50.24	50.24	50.24
Dextromethorphan Hydro bromide	188.4	188.4	188.4
HPMC E5 LV	100	100	100
HPMC E15 LV	-	-	-
HPMC 3 cps	-	-	-
PEG 400 (ml)	**2.0**	**3.0**	**5.0**
Sachharin sodium	20	20	20
Citric acid	30	30	30
Water (ml)	20	20	20

Table 5.4: Taste masking of drug using Ion Exchange Resin

Ingredients (mg)	**F4**	**F5**	**F6**	**F7**
Chlorpheniramine maleate	50.24	50.24	50.24	50.24
Dextromethorphan Hydro bromide	188.4	188.4	188.4	188.4
HPMC E5 LV	100	100	100	100
HPMC E15 LV	-	-	-	-
HPMC 3 cps	-	-	-	-
Kyron T-104	**120**	**180**	**240**	**300**
PEG 400 (ml)	3.0	3.0	3.0	3.0
Saccharin sodium	20	20	20	20
Citric acid	30	30	30	30
Water (ml)	20	20	20	20

***(All the quantities are in mg)**

Table 5.5: Screening of Amount of polymer in mouth dissolving film

Ingredients (mg)	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**	**F19**
Chlorpheniramine maleate	50.24	50.24	50.24	50.24	50.24	50.24	50.24	50.24	**50.24**	50.24	50.24	50.24
Dextromethorphan Hydro bromide	188.4	188.4	188.4	188.4	188.4	188.4	188.4	188.4	**188.4**	188.4	188.4	188.4
HPMC E5 LV	**300**	**-**	**-**	**250**	**-**	**-**	**200**	**-**	**-**	150	**-**	**-**
HPMC E15 LV	**-**	**300**	**-**	**-**	**250**	**-**	**-**	**200**	**-**	**-**	**150**	**-**
HPMC 3 cps	**-**	**-**	**300**	**-**	**-**	**250**	**-**	**-**	**200**	**-**	**-**	**150**
Kyron T-104	240	240	240	240	240	240	240	240	**240**	240	240	240
PEG 400 (ml)	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	**3.0**	3.0	3.0	3.0
Saccharin sodium	20	20	20	20	20	20	20	20	**20**	20	20	20
Citric acid	30	30	30	30	30	30	30	30	**30**	30	30	30
Water (ml)	20	20	20	20	20	20	20	20	**20**	20	20	20

Table 6.1: screening of amount of plastisizer content in fast dissolving film

Ingredients	**F1**	**F2**	**F3**
PEG 400 (ml)	**2.0**	**3.0**	**5.0**
Conclusion	***Brittle film formed***	***Good flexibility of film***	***Sticky film formed***

Table 6.2: screening of amount of Ion Exchange Resin

Evaluation parameters	**F4**	**F5**	**F6**	**F7**
Thickness (mm)	**<1**	**<1**	**<1**	**<1**
Disintegration Time (sec)	59	65	**76**	84
Surface pH	6.8	7.1	**6.9**	7.0
% Drug release in 10 min	69.8	59.4	**81.6**	72.1

Table 6.3.1: Evaluation of F8-F19 for Weight variation and thickness

Formulation	Weight variation ± S.D (mg)	Thickness ± S.D (mm)
F8	75 ± 4	1.51 ± 0.11
F9	77 ± 2	1.53 ± 0.16
F10	76 ± 6	1.52 ± 0.14
F11	73 ± 4	1.52 ± 0.18
F12	71 ± 8	1.49 ± 0.17
F13	72 ± 3	1.50 ± 0.16
F14	71 ± 4	1.51 ± 0.11
F15	72 ± 2	1.49 ± 0.12
F16	**69 ± 1**	**1.48 ± 0.16**
F17	68 ± 2	1.49 ± 0.10
F18	70 ± 6	1.50 ± 0.12
F19	68 ± 5	1.50 ± 0.16

Table 6.3.2: Evaluation of F8-F19 for folding endurance

Formulation	Folding endurance ± S.D
F8	305 ± 20
F9	302 ± 26
F10	330 ± 19
F11	328 ± 10
F12	298 ± 16
F13	269 ± 29
F14	284 ± 35
F15	268 ± 19
F16	273 ± 25
F17	271 ± 15
F18	281 ± 09
F19	272 ± 26

Table 6.3.3: Evaluation of F8-F19 for Surface pH

Formulation	Surface pH ± SD
F8	6.7 ± 0.5
F9	6.9 ± 0.4
F10	7.0 ± 0.2
F11	7.1 ± 0.3
F12	7.2 ± 0.4
F13	7.0 ± 0.8
F14	6.9 ± 0.7
F15	6.8 ± 0.5
F16	**6.7 ± 0.6**
F17	6.9 ± 0.4
F18	6.9 ± 0.4
F19	6.8 ± 0.3

Table 6.3.4: Evaluation of F8-F19 for % Drug Content

Formulation	Drug Content % ± SD
F8	99.5 ± 0.5
F9	98.8 ± 0.9
F10	99.7 ± 0.2
F11	99.6 ± 0.8
F12	98.3 ± 0.7
F13	97.8 ± 0.6
F14	100.1 ± 0.6
F15	99.3 ± 0.7
F16	**99.4 ± 0.9**
F17	98.6 ± 0.7
F18	98.7 ± 0.8
F19	98.6 ± 0.5

Table 6.3.5: Evaluation of F8-F19 for Tensile Strength and % Elongation

Formulation	Tensile Strength ± SD (N/mm^2)	% Elongation ± SD
F8	2.12 ± 0.2	60.74 ± 0.3
F9	2.10 ± 0.5	78.40 ± 0.5
F10	2.84 ± 0.7	79.12 ± 0.7
F11	2.04 ± 0.8	65.41 ± 0.3
F12	2.06 ± 0.9	59.41 ± 0.9
F13	2.12 ± 0.4	62.45 ± 0.8
F14	1.98 ± 0.7	49.18 ± 0.9
F15	1.96 ± 0.8	51.84 ± 0.4
F16	1.98 ± 0.3	52.63 ± 0.8
F17	1.96 ± 0.5	49.65 ± 0.3
F18	2.00 ± 0.5	43.51 ± 0.4
F19	1.98 ± 0.6	52.13 ± 0.7

Table 6.3.6: Evaluation of F8-F19 for In-vitro disintegration time

Formulation	In-vitro disintegration time ± SD (sec)
F8	83 ± 9
F9	95 ± 12
F10	85 ± 9
F11	98 ± 14
F12	62 ± 11
F13	78 ± 12
F14	84 ± 8
F15	79 ± 12
F16	**26 ± 10**
F17	45 ± 11
F18	85 ± 16
F19	69 ± 5

Table 6.3.7: Evaluation of F8-F19 for *In-vitro*drug release Chlorpheniramine maleate

% Drug Release in Time (min)								
Formulation	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**20**
F8	10.15	19.48	25.14	45.87	59.48	79.15	81.47	85.48
F9	9.15	16.94	35.48	56.74	62.4	69.48	71.48	76.84
F10	12.54	19.51	26.14	32.15	48.56	59.62	76.41	81.01
F11	6.84	12.54	19.57	29.48	34.45	45.21	51.36	65.14
F12	21.48	36.48	49.74	59.32	74.96	81.49	88.79	89.14
F13	12.54	20.45	32.64	49.45	53.12	64.89	69.74	81.5
F14	15.21	19.32	26.54	39.87	59.71	69.45	76.9	86.4
F15	5.32	16.24	30.54	36.4	49.7	56.8	79.5	80.4
F16	**38.45**	**60.15**	**86.74**	**97.12**	**99.64**			
F17	13.48	26.78	36.94	49.87	66.58	76.95	79.48	86.6
F18	16.32	28.45	46.98	55.52	65.62	74.65	80.87	83.54
F19	9.65	15.21	19.54	32.45	41.65	53.14	70.54	78.9

Table 6.3.8: Evaluation of F8-F19 for *In-vitro*drug release of Dextromethorphan Hydrobromide

% Drug Release in Time (min)								
Formulation	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**20**
F8	10.4	18.7	26.9	30.6	35.8	45.45	59.15	78.12
F9	15.4	20.6	39.4	43.5	45.78	68.12	79.14	86.12
F10	10.3	18.4	22.9	27.8	30.8	58.5	74.2	89.4
F11	12.4	19.7	26.7	30.5	33.15	50.89	54.15	75.19
F12	8.9	11.6	20.5	25.12	36.14	42.87	58.9	69.12
F13	16.7	23.4	35.9	45.12	56.14	70.15	81.24	87.15
F14	15.9	26.7	31.8	37.50	41.21	49.15	59.14	71.15
F15	20.5	28.7	31.5	39.14	48.12	58.15	68.14	75.14
F16	**35.1**	**52.1**	**79.8**	**89.7**	**98.5**			
F17	11.5	20.9	31.8	39.9	44.15	54.14	68.71	74.17
F18	12.9	21.7	31.6	33.8	37.52	48.15	59.17	66.14
F19	6.7	15.8	24.6	32.8	39.41	41.15	68.98	78.41

Table 6.4: Results of the stability studies F17

Time period	Weight variation (mg)	Surface pH	Drug Content (%)	*In-vitro* Disintegration time (Seconds)
Initial	75 ± 5	6.9 ± 0.5	99.8 ± 0.2	26 ± 10
After 1 Month	78 ± 7	6.7 ± 0.4	99.5 ± 0.7	27 ± 5

Time period	*In-vitro* drug release of Chlorpheniramine maleate in 10 min	*In-vitro* drug release of Dextromethorphan Hydrobromidein 10 min
Initial	99.6 ± 0.7	98.5 ± 0.5
After 1 Month	99.2 ± 0.2	99.3 ± 0.8

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