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Preparation and Evaluation of Sustained Release Tablet of Cyproheptadine Hydrochloride Using Carbopol and HPMC

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In the present work, an attempt was made to formulate sustained release tablets for antihistaminic drug Cyproheptadine hydrochloride using Carbopol 934 and HPMC E15. The tablets were prepared by direct compression process. A 32 full factorial design was employed for the optimization of developed formulation considering concentration of carbopol 934 and HPMC E15 as independent variables with drug release as dependent variables. The developed formulations showed uniform thickness, average weight, adequate hardness, drug content and friability. In vitro drug release study was carried out in simulated gastric fluid (0.1 N HCl) for the first 2 h and in phosphate buffer (pH 6.8) for the next 10 h. It can be seen that by increasing the polymers concentration, the rate of drug released from the tablet decreased dramatically. Design expert software® was used to give the solution for optimized formulation based on the evaluation of the developed formulations. Stability studies (40±2ºC/75±5%RH) for 3 months indicated that no appreciable difference was observed for the drug content and drug release.

Keyword: Sustained Release Tablet; Cyproheptadine Hydrochloride; Optimization; Carbopol; HPMC.

1. Introduction: Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled release system. If it unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system. [1]
Cyproheptadine hydrochloride is a sparingly water soluble antihistaminic agent. Cyproheptadine is rapidly and extensively absorbed and eliminated. The half-life of the drug is 3-4 hrs. in plasma, required repeated administrations of high doses to maintain effective plasma concentration, thus reducing patient compliance and/or enhancing the incidence of side effects. Sustained release system of Cyproheptadine hydrochloride, developed in order to overcome these problems.[2, 3]

The present study, aim towards the development of sustained release of drug from the tablet by direct compression. Considering different formulation variables,3^2 full factorial designs was employed for the selection of the optimized formulation from the drug release profile, considering the cost of drug by

reducing the drug dose and increasing its effectiveness and deliver drug at near constant rate.

2. Materials and Methods:

Cyproheptadine Hydrochloride was kindly supplied by Wamsi (Mumbai, India) and Carbopol 934 and HPMC E15 were kindly donated by Colorcon Asia (Goa, India). Dibasic calcium phosphate, magnesium stearate and purified talc were purchased from Loba chemie (Mumbai, India). All other ingredients and reagents were of reagent grade.

2.1 Experimental Design[4]:

A number of preliminary experiments were conducted to determine the formulation and parameters by which the process resulted in sustained released tablet. Design expert software® (Design Expert trial version 8.0.1; State-Ease Inc., Minneapolis, MN, USA) was used in our study for to optimize the concentration of Carbopol 934 and HPMC E15. A two-factor, three-level, full factorial design was employed for the optimization procedure. The amount of Carbopol 934 (X_1, % w/w) and HPMC E15 (X_2, % w/w), were selected as the independent variables i.e. factors. The levels of these factors were selected on the basis of initial studies and observations. The amount of Cyproheptadine Hydrochloride released (Y_1, percent) were chosen as the dependent variables. Table 1summarizes these factors with corresponding levels and the responses studied, whereas experimental formulations are listed in Table 2.

Table 1: Two factors, three levels full factorial experimental design; factors selected and response measured.

Factors (Independent variables)	Levels			Response (Dependent variable)
	(-1)	(0)	(+1)	
Amount of Carbopol 934 (% w/w)	2.5	5	7.5	Cyproheptadine Hydrochloride released (percent)
Amount of HPMC E15 (% w/w)	5	10	15	

Table 2: Cyproheptadine Hydrochloride sustained released formulations as per the 3^2 Experimental designs

Ingredients (mg)	D1	D2	D3	D4	D5	D6	D7	D8	D9
Cyproheptadine hydrochloride	5.24	5.24	5.24	5.24	5.24	5.24	5.24	5.24	5.24
Carbopol 934	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5
HPMC E15	5	10	15	5	10	15	5	10	15
Dibasic calcium phosphate	85.96	80.96	75.96	83.46	78.46	73.46	80.96	75.96	70.96
Talc	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total weight	100	100	100	100	100	100	100	100	100

2.2 Preparation of sustained release matrix tablets:

All the tablet formulation was prepared by using wet granulation technique. Starch was accurately weighed and dissolved in slightly warmed doubled distilled water. All excipients except magnesium stearate and purified talc were accurately weighed and passed through 40# sieve. Calculated amount of drug, polymers and filler dibasic calcium phosphate were mixed thoroughly. A sufficient amount of granulating agent was added slowly to achieve the granulation endpoint. After enough cohesiveness was obtained, granules were dried at 50^0c for 30 minutes. The semi-dried granules were passed through 10# sieve and drying was continued for another 1 hour and 30 minutes. The granules were collected and passed through #20 sieves.

Magnesium stearate and purified talc was passed through 80# sieve to lubricate the granules. The granules were compressed using 6mm round standard concave punches. The composition of the different formulation as per the Experimental design is shown in table 2.

2.3 Evaluation of granules and sustained released tablet[3, 5, 6, 7]:

Granules ready for compression prepared by wet granulation method were evaluated for flow properties like Bulk density, Tapped density, Carr's index and Hausner's ratio.

The hardness of tablets (n=6) were determined by using Tablet strength tester (Monsanto, 13-1). The friability (n=10) of the tablets was determined using a USP-I friabilator (EF 1W; Electrolab), and uniformity of tablet weight (n=20) was evaluated as per pharmacopeial guidelines. Thickness (n=3) of the tablets was determined by using vernier calipers (Mitatoyo, Japan) and drug content of the tablet was assayed in triplicate using validated UV-Spectrophotometer (Jasco, V-630) method.

2.4 ***In vitro*** **Release Study[2, 8]:**

Dissolution test was performed on six tablets from the formulation accepted by friability and hardness tests. The dissolution USP apparatus II (Electrolab, model TDT-08L, Mumbai, India) using 900ml of 0.1N HCL maintained at 37± 0.5^0C stirred at 50 rpm for 2 h. Then the same tablets were removed and placed in 900 ml of phosphate buffer p^H 6.8 as dissolution media maintained at 37± 0.5^0C. A 5ml sample was withdraw through a 0.45µm syringe filter and replaced with another 5ml of a suitable fresh dissolution medium at pre-selected intervals up to 12 hrs. The amount of drug released was then determined with the help of calibration curve and the cumulative percentage of drug released was calculated.

2.5 Stability study[9]:

The stability of optimized formulations was tested according to ICH guidelines. The formulations were stored at accelerated (40±2°C/75±5% RH) test conditions in stability chamber (Remi, CHM-6S) for three month. At the end of month, tablets were tested for drug content and percent drug released.

3. RESULTS AND DISCUSSION:

In the present work, an attempt has been made to prepare sustained released matrix tablets of Cyproheptadine hydrochloride, an antihistaminic agent by combining two different polymers namely Carbopol 934 and HPMC E15 by wet granulation method. The prepared granules ready for compression tested for flow properties like Bulk density, Tapped density, Carr's index and Hausner's ratio. The prepared tablets were tested for physical parameters like hardness, weight variation, friability, thickness, drug content and *in vitro* drug released study. The results of all these evaluation are given in table 3 to 5.

Table 3: Physical evaluation of granules of nine formulations as per the experimental design

Formulation code	Parameters			
	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index	Hausner's ratio
D1	0.52±0.0057	0.59±0.0057	10.2±0.1154	1.11±0.00173
D2	0.52±0.0057	0.55±0.0069	9.9±1.06	1.10±0.0115
D3	0.55 ±0.0115	0.61±0.0069	9.2±0.923	1.10±0.0115
D4	0.53±0.0057	0.58±0.0057	10.3±0.929	1.115±0.0092
D5	0.55±0.0057	0.61±0.0059	11.4±0.346	1.12±0.0057
D6	0.54±0.005	0.60±0.004	10.2±0.9814	1.11±0.112
D7	0.52±0.0057	0.58±0.0057	10.3±0.1157	1.11±0.0011
D8	0.56±0.0057	0.625±0.0086	10.4±0.346	1.12±0.0057
D9	0.55±0.0057	0.62±0.0086	12.1±0.346	1.13±0.0057

Note: Mean of 3±SD

Table 4: Physical evaluation of Cyproheptadine hydrochloride sustained released formulations

Formulation code	Weight variation[a](mg)	Thickness[b] (mm)	Hardness[c] (kg/cm^2)	Friability[d] (%)	Drug content[e] (%)
D1	100.51±4.5	2.28±0.0057	5.33±0.56	0.69±0.12	99.42±0.19
D2	101.31±3.9	2.29±0.0059	5.48±0.19	0.26±0.18	99.47±0.84
D3	100.10±3.7	2.27±0.0057	5.43±0.89	0.29±0.70	98.28±0.86
D4	99.24±2.6	2.26±0.0057	4.98±0.17	0.58±0.65	98.85±0.36
D5	101.65±1.9	2.27±0.0059	6.12±0.18	0.31±0.48	99.19±0.24
D6	100.31±4.5	2.28±0.0057	5.74±0.39	0.26±0.28	99.23±0.22
D7	100.21±3.5	2.26±0.007	5.62±0.09	0.60±0.57	98.74±0.54
D8	100.45±1.2	2.29±0.0059	5.19±0.21	0.46±0.19	99.04±0.49
D9	100.0±1.4	2.26±0.007	6.02±0.31	0.76±0.52	98.44±0.43

Notes: [a]Test performed on number of tablets weighing not less than 2 gm, [b]Mean of 3±SD, [c] Mean of 6±SD, [d]Test performed on 20 tablets and [e]Mean of 3±SD.

Table 5: In vitro release data of Cyproheptadine hydrochloride sustained released tablet

Time (Hrs)	% Cumulative drug release								
	D1	D2	D3	D4	D5	D6	D7	D8	D9
1	11.85	10.12	9.45	8.82	7.52	7.07	8.2	7.96	7.2
2	25.36	18.6	18.60	18.17	16.40	12.85	17.72	17.25	11.97
3	39.38	33.25	29.53	31.45	26.68	22.08	26.42	28.15	20.78
4	51.48	44.69	41.80	40.56	36.78	29.04	34.30	36.98	29.06
5	60.28	53.89	53.08	49.25	44.89	39.56	43.51	44.12	36.52
6	69.48	63.46	60.12	57.25	52.34	45.77	51.89	51.27	44.02
7	76.41	72.05	68.32	65.34	59.34	51.15	60.31	58.72	49.82
8	87.53	80.56	76.62	70.94	65.46	56.55	68.53	65.16	55.21
9	97.30	88.67	82.56	77.29	72.37	61.97	78.13	70.19	60.19
10	-	95.10	89.31	87.54	77.46	66.98	86.66	76.57	65.63
11	-	-	95.82	95.69	85.99	71.15	94.37	85.04	70.66
12	-	-	-	-	93.26	78.36	99.09	90.59	75.71

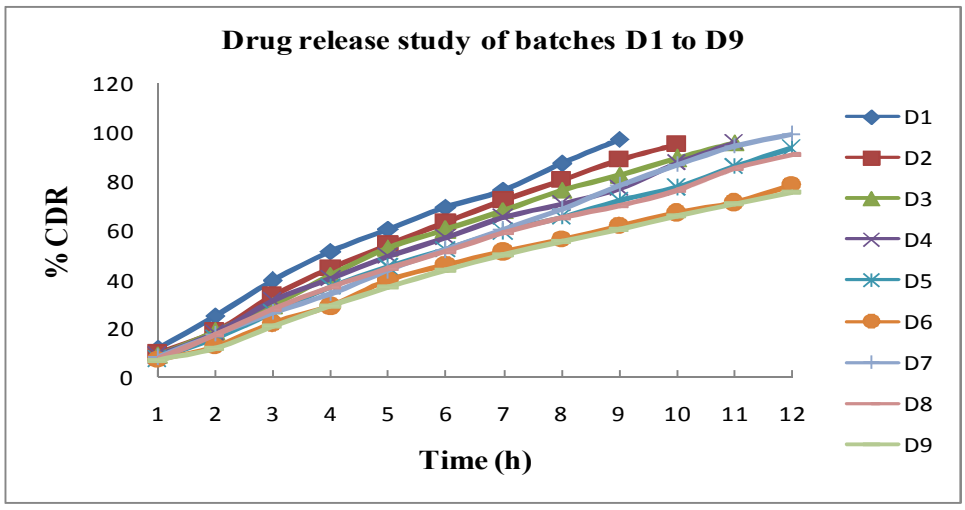
From the physical evaluation results (Table 3) of granules prepared by wet granulation method, it is clear that the granules has a good flow properties, which is a sign to indicate the suitability of the granules for a direct compression formulation.

All the prepared tablets were evaluated for weight variation and results are given in table 4. The percent deviation from the average weight was found to be within the prescribed official limits. Hardness of tablets was found to be in the range of 4.98±0.17 to 6.12±0.18 kg/cm^2 and is given in table 3. The friability of all the prepared tablets was found to be in the range of 0.26±0.18 to 076±0.52 %, fulfilling the official requirements (not more than 1%). Drug content estimation data for all batches was found to be in the range of 98.44±0.43 to 99.47±0.84 %, indicate uniform drug content in the tablet. The thickness of prepared tablet was found to be in the range of 2.26±0.007 to 2.29±0.0059 mm, indicate uniform thickness of tablet.

The carbopol 934 and HPMC E15 has been well known to ratard the drug release by swelling in

aqueous media. A polymers ability to retard the drug release rate is related to its viscosity, processing factors including particle size, hardness, porosity and compressibility index etc. also can affect the release rate of drug from tablets. The hydration rate of HPMC depends on the nature of the substitute like hydroxyl propyl group content.HPMC E15 used because it forms a strong viscous gel in contact with aqueous media. The drug release data were shown in table 5 and in vitro drug release profile were shown in figure 1. It can be seen that by increasing the polymers concentration, the rate of drug released from the tablet decreased dramatically.Because tablets containing hydrophilic polymers absorb water and swell, the polymer level in the outermost hydrated layers decreases with time. The polymer chains break away from the matrix when the surface concentration passes a critical polymer concentration of macromolecular disentanglement or surface erosion. The polymer concentration at the matrix surface is defined as the polymer disentanglement concentration[10]. It was observed that higher polymer levels result in slower release rates as evident from the in vitro drug release profile of all batches.In all formulations as the concentration of HPMC E15 increased, the release rate is decreased; this is possibly due to the increased viscosity of carbopol 934, which might have helped to keep the hydrated gel intact, releasing the drug for 12 hrs. Among all formulations, D7 containing 7.5 % and 5% concentration of carbopol 934 and HPMC E15 respectively showed 99.0.9% release in 12 hrs.

Figure 1: Dissolution profile for all nine formulations as per the factorial design



The data obtained from in vitro dissolution studies when put into design expert software, software gives one desirable solution, that when we used 7.5% and 5% of carbopol 934 and HPMC E15 respectively, it is expected that the developed formulation should have the maximum drug release profile for 12 hrs. The optimized formulation was prepared and subjected to evaluation, table 6, 7 showed the composition and in vitro dissolution data for the optimized formulation. The result of the dissolution data of optimized formulation revealed that, 18.45% drug release at the end of 2 hrs and 99.19 % of drug release at the end of 12 hrs.

Table 6: Composition for optimized formulation

Ingredients	Quantity(mg)
Cyproheptadine hydrochloride	5.24
Carbopol 934	7.5
HPMC E15	5
Dibasic calcium phosphate	80.96
Talc	0.8
Magnesium stearate	0.5
Total weight	100

Table 7: In vitro dissolution data for optimized formulation

Time (Hrs.)	% Cumulative drug release
1	8.84±0.56
2	18.45±0.89
3	30.35±0.49
4	41.28±0.38
5	48.12±0.84
6	56.79±0.53
7	63.56±0.46
8	71.85±0.88
9	78.13±0.79
10	86.66±0.91
11	93.68±1.08
12	99.09±0.43

Note: Mean of 3±SD

The results of accelerated stability study carried out according to ICH guidelines, indicates that the drug content and drug release was found to be 98.55% and 98.34 at the end of 3 months respectively. No appreciable difference was observed for the above parameters (Table 8).

Table 8: Accelerated stability study analyzed data (40±2°c/75±5% RH)

Stability	Drug content (%)	Drug release (%)
Initial	98.87±0.98	99.09±2.15
1 month	98.75±1.23	98.83±1.68
2 month	98.67±1.54	98.36±1.72
3 month	98.55±0.86	98.34±1.44

Note: Mean of 3±SD

4. CONCLUSION:

This study deals with the investigations carried out with the objective of developing oral sustained release formulations for the widely used antihistaminic drug Cyproheptadine hydrochloride using polymers Hydroxy propyl methyl cellulose E15, Carbopol 934 and evaluation of their sustained release potential. Based on above results and discussion, it is concluded that the formulated tablets of

Cyproheptadine hydrochloride using HPMC E15 and Carbopol 934 were capable of exhibiting sustained release properties. They are thus capable of reducing the dose intake, minimize the blood level oscillations, dose-related adverse effects and cost thus ultimately improve the patient compliance.

5. REFERENCES:

1. Shantveer VS, Lingaraj SD, Shivanand H and Abdul S. Preparation and evaluation of sustained release matrix tablets of propranolol hydrochloride. 2010; 1(4): 227-241.
2. The Merck Index. 2001. An encyclopedia of chemicals, drugs and biological, 13th edition, Merck and Co. Inc. NY pp. 542.
3. Indian Pharmacopeia: Controller of Publication, Ministry of Health and Family Welfare, Government of India, Delhi; 2007. P.477-478, 1020-1021.
4. Bolton S. Pharmaceutical statistics practical and clinical applications.3rd edition. Marcel Dekker publisher. New York, USA: 326-351, 591-626, (1997).
5. Aulton ME. The design and manufacture of medicines, Aulton's Pharmaceuticals, 3rd edition, *Churchill Livingstone Elsevier Publisher:* 175-177, 465-466, (2007).
6. British Pharmacopeia: Medicine and Health care Regulatory Agency, Government of UK: Vol-II, P.A-244, A-260, A-267, (2005).
7. Lachman L, Lieberman H and Kanig J. The Theory and Practice of Industrial Pharmacy, 3rd Edition,Bombay,*Varghese Pubilishing House:*299-301,303-309, (1990).
8. Sweetman SC, Martindale. The complete drug references, 33rd Ed., Pharmaceutical press 2002; 897.
9. Ali J, Khar RK and Ahuja A. A Textbook of Dosage form design. Birla Publications Pvt. Ltd. 3rd Ed., 2008; 114-116.
10. Raghavendra NG, Gandhi S and Patel T. Formulation and evaluation of sustained release matrix tablets of tramadol hydrochloride. *Int J pharm tech*. 2009; 1(1): 60-70.