AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation and *in-vitro* Evaluation of Ciprofloxacin Hydrochloride Sustained Release Tablets using various Viscosity Grades of Hydroxypropyl Mythylcellulose

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ABSTRACT

The primary objective of sustained release drug delivery system is to ensure safety and to improve efficacy of drugs as well as patient compliance. Using controlled drug delivery system the drug release pattern can be controlled within narrow therapeutic range, which leads to minimize the side effect and ensure the safety. The aim of the study is to design, characterize and evaluate ciprofloxacin hydrochloride sustained release tablets using various viscosity grades of HPMC. As ciprofloxacin HCl has very short half life (nearly 3½ to 4 hr) hence multidose therapy for conventional tablets, (250 mg, 500 mg twice a day) is necessary to get the desired therapeutic level. Hence in the presence study attempt has been made to formulate the sustained release tablets of ciprofloxacin HCl using different viscosity grades of HPMC i.e. HPMC K4m, HPMCK_{15}M, HPMC K_{100}M with different drug polymer ratio to reduce the dosing frequency, minimize the flections of plasma drug concentration, evaluation has been done of the prepared formulation and compared with the standard. The prepared granules were free flowing and characterized for drug content, DSC, X-ray diffraction study and FTIR. The X-ray diffraction study & DSC obtained from various formulations showed no interaction within these formulations. The in-vitro release studies were performed using pH 7.4 phosphate buffer for 12 hours from which the different drug polymer ratios are followed zero order kinetics.

Keywords: Differential Scanning Calorimetry, X-ray diffraction study, Hydroxyl propyl Methyl Cellulose, zero order kinetics

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Received 12 July 2013, Accepted 19 July 2013

Please cite this article in press as: Padhy S. *et al.*, Formulation and *in-vitro* Evaluation of Ciprofloxacin Hydrochloride Sustained Release Tablets using various Viscosity Grades of Hydroxypropyl Mythylcellulose . American Journal of PharmTech Research 2013.

INTRODUCTION

The term 'Sustained Release' is known to have existed in the medical and pharmaceutical literature for many decades. Sustained release has been constantly used to retard the release of therapeutic agent such that its appearance in the circulation is delayed / prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed and duration of therapeutic action is sustained. [1]

The major objectives of the novel controlled release drug delivery system are to fulfill the entire therapeutic requirement and increasing patient compliance.[3] Generally a dosage form consists of one or more active ingredient together with a varying number of other substances (excipients). These excipients enomorously influence the physico-chemical characteristic of the final product. It is now recognized that the excipients can potentially influence the rate and extent of absorption of a drug.[6] Therefore a well established formulation depends on the careful selection of excipients.[2] By reviewing the present and past scenario, it is never worthless to mention the use of polymer as a formulation aid in sustained drug delivery systems become are important area of research and development. [5, 7, 8]

MATERIALS AND METHODS:

Materials:

Ciprofloxacin HCl was obtained as gift sample from Dr. Reddy's lab, Hyderabad. HPMC K4M, K15M, K100M were obtained from M/s Ranbaxy Lab, Gurgaon.[14, 21] PVP, IPA, Sodium Hydrogen Pellet Purified were collected from CDH Pvt. Ltd., New Delhi. Magnesium Stearate and Lactose Monohydrate were received from Lobachem, Pvt. Ltd. Mumbai. Potassium Dihydrogen Orthophosphate was collected from S.D. Fine Chemicals, Mumbai. Other chemicals were of analytical reagent grade**.** [18]

Apparatus & Equipments:

The UV/ VIS. Spectrophotometer is of Elico, India Ltd., Dissolution Apparatus is of USP 8 basket Digital Test Apparatus Lab India (Disso-2000) Mumbai., Mechanical Sieve Shaker is of Comprit Electrical Company India, Sieve set is of ASTM Standard Sieves, SISSO, India, Tablet Compression Machine (Single Station) is of Cadmach Machinery Co. Pvt. Ltd., India., Roche friabilator is of Rolex Pvt. Ltd., India., Tablet hardness Tester is of Cadmach Machinery Co. Pvt. Ltd., India., Tray Drier is of Rolex Pvt. Ltd., India , Single Pan Balance is of Adair Dutta AD –50 B, Kolkata., DSC is of Mettler Star^{e} SW 8.01, FTIR is of Parkin Elmer (Paragon), Distillation Apparatus and Glass ware, pipette, beakers, volumetric flask is of Borosil type. [17]

Standard Curve:

Various concentrations were prepared by suitable diluting working standard solution with 0.1 N HCl. The optical densities of these solutions were measured at 278nm using U.V[23] Visible spectrophotometer. Then the standard plot of Absorbance VS Concentration was drawn from the data. Similarly the process was repeated in distilled water at 277 nm. [27]

Sieve analysis:

An accurately weighed 2 gm quantity of drug (Ciprofloxacin HCl) was subjected to granulometric study using sieves 22, 44, 60, 80, and 100 using a sieve shaker. Drug is sieved nearly around 10 minutes than the sieves are removed from the sieve shaker and powder retained in each sieves was calculated in percentage form using initial weight taken. [28]

Physico-chemical Characterization of the Drug:

The drug was characterized for Density Measurement i.e. Bulk density, Tapped density, Flow property i.e. Angle of Repose, Carr's index and Hausner's Ratio.[33]

FTIR Study:

FTIR study was carried out to identify the drug samples in Alkem Laboratories, Daman, using PARKIN – ELMER FTIR by preparing Potassium Bromide pellet of the sample using Potassium Bromide press. [35] The IR spectrum of the sample of pure drug was preliminary identification of the sample by comparing it with reference standard. The sample give exact absorbance peaks with standard hence the sample is in pure form.[36]

DSC Study:

Generally DSC studies are done to know whether any physical in compatibility exists or not between the drug with various excipients to be used. So DSC studies of individual drug and mixture of each excipient with drug in 1: 1 ratio was studied to see whether any interaction exists or not. In the present study no significant interaction was found between the drug and excipients. In this study, the samples were run from 30^0C to 450^0C as 10^0c/min in a METTLER STAR^{e}SW 8.01 DSC analyzer and the thermo gram was obtained. [6] The peak was analyzed for its onset and melting point. Generally ± 10^0C deviation from actual thermo gram is permitted, i.e. it shows no significant interaction with drug.[34]

Formulation:

All the formulations were formulated by wet granulation method. Different viscosity grades of HPMC such as HPMC K4M, HPMC K15M and HPMC K100M are used in the study. Binders used in granulation were PVPK30 and Isopropyl alcohol (as binder solution).First Ciprofloxacin HCl, HPMC of suitable grade (both passed through # 60) and lactose were weighed according to

the formula given in the table No.13 and mixed properly. [5 PVPK30 was weighed and dissolve in 10 ml of IPA then stirred properly in a mechanical stirrer. Wet granulation was done by adding small amount of PVPK30 solution to the mixture to prepare damp mass. Damp mass is then passed through # 10 for granulation. Dried for 30 minutes at room temp in open air. Then kept in the tray drier for 2 hrs at 40^0C.The dried granules again passed through # 16. Then lubricated using magnesium stearate. After that granules were compressed by single paunch cadmach tablet compression machine with 12 mm punch.[43]

Table 1: Sieve analysis of Ciprofloxacin HCl Bulk drug

Sieve No.	Drug retained on sieve	% weight retained	Cumulative percentage retained
22	55 mg	3.85	3.85%
44	870 mg	61.05	64.9%
60	155 mg	10.87	75.77%
80	250 mg	7.54	93.31%
100	95 mg	6.66	99.97%

Table 2: Illustration of Physico chemical characteristics of the Ciprofloxacin HCl

Experiment	Result
Bulk density	0.263 g/cc
Tapped density	0.454 gm/cc
Carr's index	42.07%
Hausner's ratio	1.726
Angle of repose	15.6
Melting point	319^0c
Assay	101.1%

Table 3: Formulation of Ciprofloxacin HCl SR tablets using different grades of HPMC

Ingredients	D:P:: 1:0.025 (F1)	D:P:: :1:1 (F2)	D:P:: 1:0.025(F3)	D:P:: 1:1 (F4)	D:P:: 1:0.025 (F5)	D:P:: 1:1 (F6)	D:P:: 1:0.025(F7)	D:P:: :1:1 (F8)	D:P:: 1:0.025(F9)	D:P:: 1:1 (F10)	D:P:: 1:0.025 (F11)	D:P:: 1:1 (F12)
Ciprofloxacin HCl	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
HPMC K4M	62.5 mg	250 mg	62.5 mg	250 mg	62.5 mg	250 mg	62.5 mg	250 mg	62.5 mg	250 mg	62.5 mg	250 mg
Lactose Monohydrate	251.5 mg	64 mg	251.5 mg	64 mg	251.5 mg	64 mg	251.5 mg	64 mg	251.5 mg	64 mg	251.5mg	64 mg
PVPK30	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg
Mag.Stearate	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg
IPA	Q.S.	Q.S	Q.S.	Q.S	Q.S.	Q.S	Q.S.	Q.S	Q.S.	Q.S	Q.S.	Q.S
Total Weight	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg

Physico chemical evaluation of prepared granules:

The prepared granules are subjected to the following characterization prior to compression as their properties were going to play the critical role in formulation of the tablets with a flawless approach.[50]

Evaluation of tablets:

The compressed tablets were evaluated for the important parameters that affect the release the drug such as weight variation, thickness, hardness, friability, tablet disintegration, drug content estimation and in vitro drug release pattern.[35]

In-vitro Dissolution Study

In-vitro dissolution studies were designed to carry out in such a way that they stimulate in vivo conditions. The purpose of in-vitro release study was to provide a fast, easily performed and in-expensive method that correlates with the performance of dosage form in human subjects. The conditions of in-vitro dissolution test were very well defined standardized and enabling comparison between various results. [53] For in-vitro dissolution study it was decided to carry out the dissolution in 0.1 N HCl. The apparatus used is USP XX Apparatus I (Rotary basket) having Sampling interval 0.5th, 2nd, 4th, 8th and 12th hr. Directly 0.9ml sample was pipetted out, filtered and diluted to 25ml with respective dissolution medium and absorbance seen directly against the blank (respective dissolution medium) using UV spectro photometer at 278nm. [52]

RESULTS AND DISCUSSION:

Ciprofloxacin Hydrochloride being a widely used broad spectrum anti-microbial drug primarily absorbs from upper part of GI tract. Organoleptic characteristics of pure drug (Ciprofloxacin Hydrochloride) showed that the drug is pure in nature.

Spectroscopy study using UV visible spectroscopy of pure drug with different mediums like 0.1N HCl, distilled water, showed that maximum wavelength was found to be 278 nm and 277nm respectively.

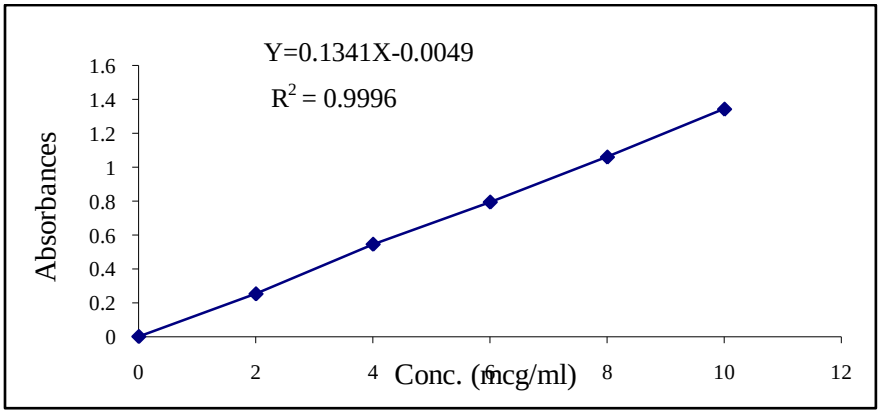


Figure-1: Calibration curve of ciprofloxacin HCl in 0.1N HCl

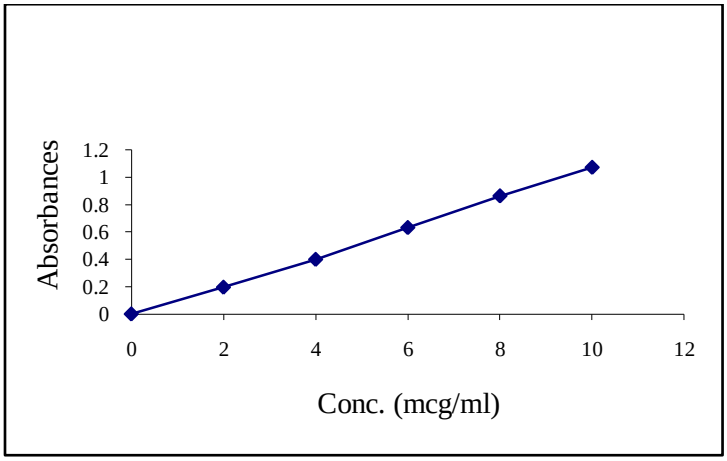


Figure-2: Calibration curve of Ciprofloxacin HCl in Distilled water

In this present investigation sustained release tablets of Ciprofloxacin Hydrochloride were prepared by wet granulation technique using various viscosity grades of HPMC like HPMC K4M, K15M and K100M.Different formulations (F1 – F6) prepared with drug and individual viscosity grades of HPMC like HPMC K4M +K15M , HPMC K4M +K100M , HPMC K15M +K100M in same ratio.

From the pre formulation aspects, compressibility index and angle of repose of all formulations the formulations having excellent flow property comparison to pure drug having poor flow property.

Table 4: Physico-chemical Properties of Ciprofloxacin HCl granules

Formulation	Bulk density	Tapped density	Carr's Index%	Hausner's ratio	Angle of repose
F1	0.354 ± 0.002	0.396 ± 0.006	10.60	1.11	22.13±0.96
F2	0.362 ± 0.007	0.398 ± 0.001	9.27	1.10	20.01±0.02
F3	0.363 ± 0.009	0.392±0.009	7.65	1.08	22.06±0.05
F4	0.350 ± 0.011	0.397± 0.005	9.84	1.10	21.07±0.11
F5	0.352 ± 0.001	0.394 ± 0.007	10.4	1.11	21.65±0.40
F6	0.353 ± 0.067	0.392 ± 0.009	9.13	1.10	20.39±0.26
F7	0.361 ± 0.007	0.3393 ±0.002	10.421	1.11	22.99±0.40
F8	0.356 ± 0.008	0.387 ± 0.008	8.46	1.09	21.96±0.14
F9	0.361 ± 0.013	0.402 ± 0.007	9.92	1.11	20.39±0.26
F10	0.349 ± 0.007	0.407 ± 0.006	13.50	1.15	21.60±0.25
F11	0.352 ± 0.001	0.386 ± 0.007	9.04	1.09	19.95±0.17
F12	0.355 ± 0.006	0.399 ± 0.007	10.5	1.11	20.86±0.26

The evaluation of tablets study reveals that all formulations carried out for physical parameters like hardness, thickness, friability, weight variation, % of drug content and drug release which shows satisfactory results.

Besides that other evaluation parameters i.e. Weight variation and Friability of tablets were within IP limits followed by Hardness & thickness.

Table 5: Evaluation Parameters of Ciprofloxacin HCl tablets

Formulation	Avg. Wt (mg) n = 20	Hardness(Kg/cm^2) n = 10	Thickness(cm) n = 10	Friability (%)n = 3	Assay (%) n = 3
F1	596.8±4.93	5.84± 0.35	0.345 ±0.049	0.001	99.06±0.065
F2	589.1±4.254	5.77 ±0.41	0.360 ±0.045	0.003	99.160±0.69
F3	595.5±4.778	5.91± 0.42	0.375 ±0.042	0.001	98.26 ±0.23
F4	596 ±5.888	5.64 ±0.38	0.355 ±0.036	0.002	99.31 ±0.31
F5	595± 4.211	5.42 ±0.33	0.345 ±0.036	0.002	99.26± 0.26
F6	588.6±6 3.566	5.41 ±0.32	0.355± 0.028	0.001	98.82 ±0.61
F7	596.6 ±5.383	6.10 ±0.37	0.304 ±0.035	0.00	101.61±0.26
F8	594.5 ±5.380	6.11 ±0.29	0.305 ±0.049	0.00	99.96 ±0.31
F9	595 ±4.219	6.55± 0.27	0.325 ±0.042	0.001	99.26± 0.26
F10	594 ±2.41	5.81± 0.31	0.350 ±0.050	0.00	99.38 ±0.29
F11	598.6 ±4.438	5.95± 0.25	0.330 ±0.040	0.001	101.62±0.11
F12	599 5.35	5.98 0.39	0.340 0.049	0.001	99.89 0.62

In-vitro dissolution study of pure drug (Ciprofloxacin Hydrochloride) and formulations was carried out with 0.1 N Hcl using basket at 100 rpm which shows that 99.59 % drug release in 60 minutes and 99.48% drug released(F7)at 12 hours.

From the dissolution data of all formulations, it is concluded that F7 (HPMC K4M +K15M, 1: 0.25) showed better reproducibility comparison to all the formulations and maintains sustained effects. All the formulations followed Zero order release Kinetics.

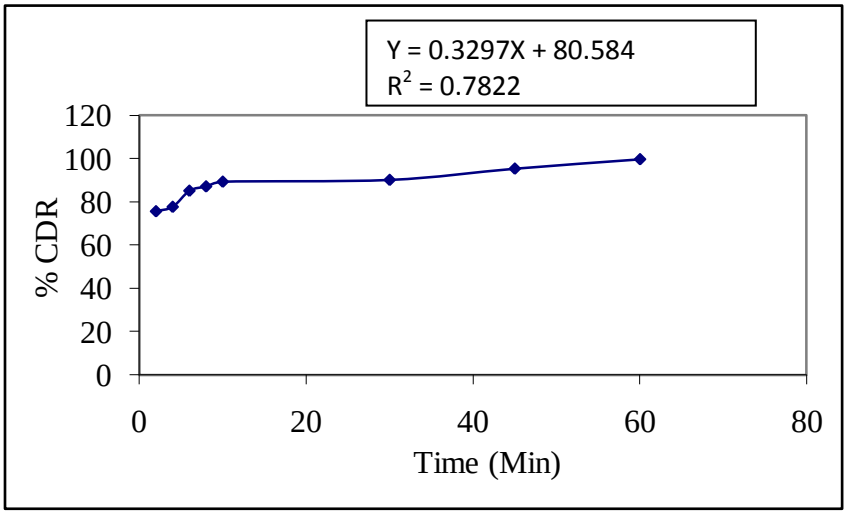
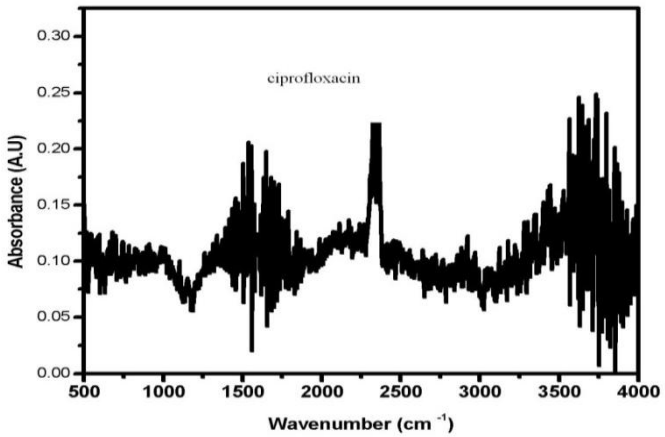


Figure-11: Percentage cumulative release of pure drug vs. time.

Table 6: Percentage cumulative release of Ciprofloxacin formulations (F1 – F12) vs. time.

Time in hrs.	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	3.723008	2.792256	2.688839	7.342599	6.308431	2.585422	5.687929	2.378588	1.137585	9.30752	0.827335	0.517084
2	18.8	16.44329	15.09887	18.8	17.3	9.6	28	25.44056	19.54579	28.8	28.23281	9.928021
4	32.8	30.1	28	32	31	27.40548	42	45.19318	35.78225	42.4	40	21.61413
8	62.67064	59.3	55.53484	62.5	58.22371	53.2597	76	71.56449	70.84057	76.8	72.5	69.39273
12	86.04286	82.31985	77.149	86.45652	83.35402	82.6301	99.48705	98.5563	96.59138	99.48705	97.00505	96.90163

The FTIR study of pure drug and polymer like different viscosity grades of HPMC showed that there is no interaction between the drug and polymers.



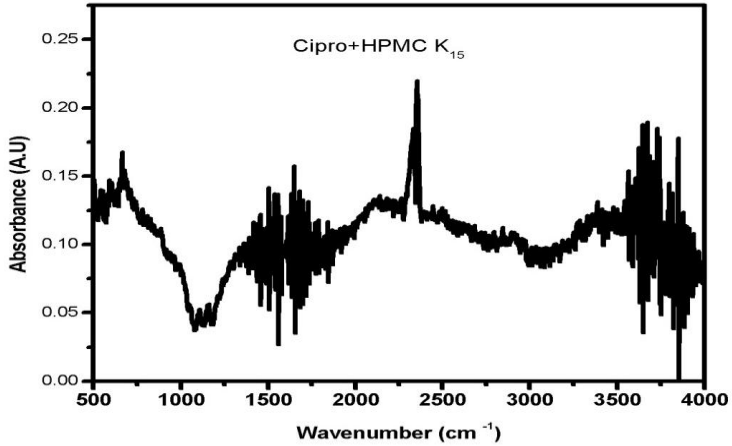


Figure-3: FTIR Study of Ciprofloxacin HCl pure drug **Figure-4: FTIR Study of Ciprofloxacin HCl pure drug and with HPMC K15M**

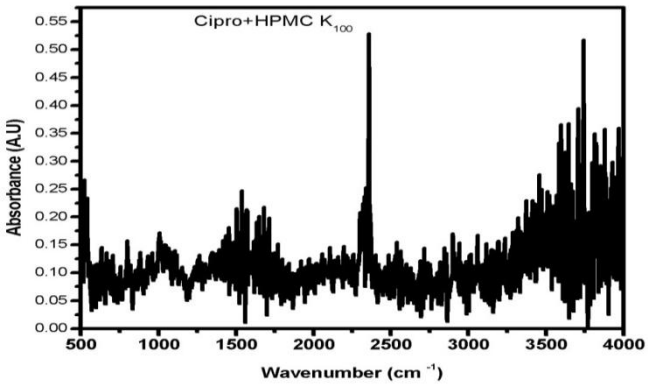


Figure-5: FTIR Study of Ciprofloxacin HCl pure drug and with HPMC K100M

The DSC study of pure drug & polymers like different grade of HPMC showed that the endothermic peak leading to melting of pure drug and formulations.

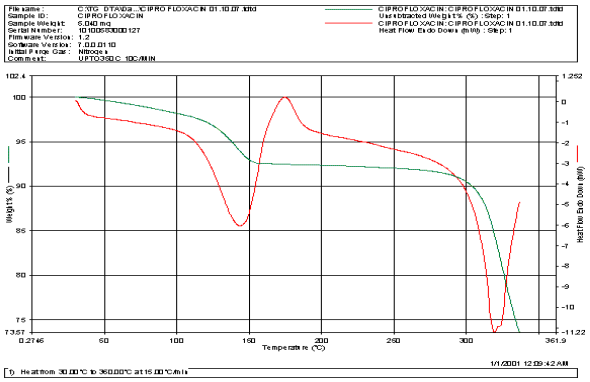


Figure-6: DSC Study graph of pure Ciprofloxacin HCl

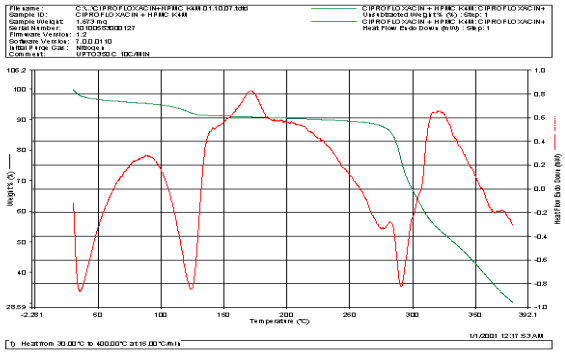


Figure-7: DSC Study graph for the mixture of Ciprofloxacin HCl and HPMC K4M

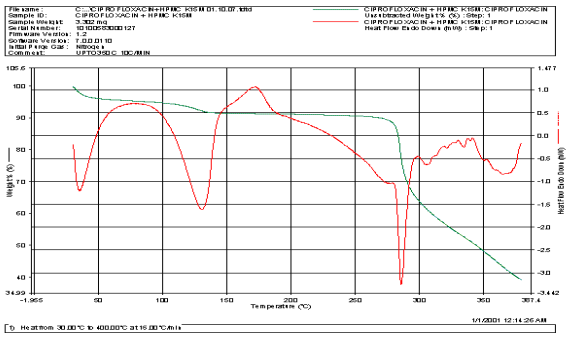


Figure-8: DSC Study graph for the mixture of Ciprofloxacin HCl and HPMC K15M

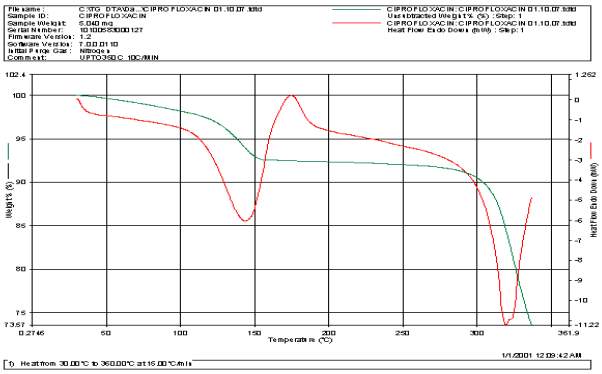


Figure-9: DSC Study graph for the mixture of Ciprofloxacin HCl and HPMC K100M

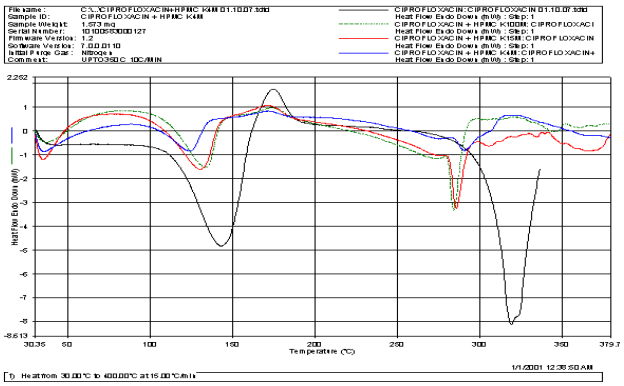


Figure-10: DSC Study of pure Ciprofloxacin HCl and drug with different grades of HPMC

CONCLUSION:

Sustained release tablets are prepared with 3 viscosity grades of HPMC like HPMC K4M, K15M and K100M by wet granulation method out of which total 12 formulations (F1 – F6) i.e. with individual polymers in different ratio and (F7 – F12) i.e. with mixture of different grades of HPMC were formulated. All these prepared formulations were evaluated for weight variation, hardness, thickness, drug content and drug release pattern which showed satisfactory results according to IP specifications. Among all the formulations F7 (HPMC K4M + K15M, 1:0.25) showed better release maintaining sustaining effect comparison to pure drug followed by Zero order kinetics of all formulations. As the result of the above study shows a promising path for development of once daily oral sustained release Ciprofloxacin HCl 250 mg tablets and as the result of the studies are giving positive sign towards successful development of desired products, it automatically shows the path for the further research towards this. So this research gives a broad horizon towards the development of a modified release preparation and comparative evaluation of their release pattern. As In-vitro dissolution gives satisfactory results, it can be further studied for In- vivo in animals and human to evaluate the dosage forms in a more precise manner. In- vivo study in normal and diseased volunteers should be done to find out the adverse

effects, pharmacokinetics parameters etc. Stability study of the final formulation should be done according to ICH guidelines to ensure the proper function of the dosage forms.

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