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Formulation and evaluation of cephalexin extended release tablets

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Abstract

The present investigation deals with development of Hydroxypropyl methylcellulose (HPMC 15cps) based cephalexin extended release (ER) tablet by direct compression method, which can release the drug for six hours at predetermined rate. Different concentration of HPMC 15cps were taken from lower to higher concentration with respect to drug and study their effect on drug release and evaluate different formulation parameters like bulk density, tapped density, compressibility index, Hausner's ratio, tablet hardness, friability, uniformity of weight, uniformity of drug content and stability study. The result of extended release tablet formulation F-5 containing 13.3% HPMC 15cps with respect to drug shows drug release in six hours at predetermined rate from other 5 formulation. The dissolution results show that on a higher amount of HPMC 15cps in tablet composition resulted in reduced drug release. The tablets were prepared by direct compression method. Hardness was found to be in the range of 7.54±0.01to 10.24±0.03 kg/cm^2, the percent friability was in the range of 0.1022±0.02 to 0.3633±0.01 % and tablets showed 97.18±0.48 to 99.78±0.07% of the labeled amount of cephalexin indicating uniformity content. The effect of storage on *in vitro* release and physicochemical parameters of successful batch was studied and was found to be in acceptable limits.

Key-Words: Cephalexin, Extended release tablet, Hydroxypropyl methylcellulose 15cps, *In vitro* dissolution

Introduction

Oral route of administration have a wide acceptance up to 50 to 60% of total drug form. Solid dosage forms are popular because of ease of administration, self medication, pain avoidance as compared with parenteral and low cost[1]. Controlled drug delivery is described as phasing of drug administration to the needs of the condition at hand so that an optimal amount of drug is used to cure or control the condition in a minimum time. Hydrophilic matrices containing swellable polymers are referred to as swellable controlled-release systems or hydrophilic matrix tablets. A number of polymers have been investigated to develop in situ gel-forming systems, due to the ability of these matrices to release an entrapped drug in aqueous medium and to regulate release of such drug by control of swelling and cross-linking. Hydroxypropyl methylcellulose (HPMC), Eudragit, Sodium alginate and Guar gum are the polymers most widely used as gel-forming agents in the formulation of solid, liquid, semisolid and even controlled-release dosage forms[2].

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Extended release dosage forms that allow at least a two fold reduction in dosage frequency as compared to that drug presented as an immediate release form. Ex: Controlled release, Sustained release[3].

Cephalexin is a semisynthetic cephalosporin β lactum antibiotic intended for oral administration used to treat urinary tract infections, respiratory tract infections, skin and soft tissue infections[4]. It is absorbed completely (80—100%) after oral administration and the protein binding of cephalexin is low (6-15%). The volume of distribution is 15±2.3 l. Cephalexin is not metabolized in the body and is excreted unchanged in the urine at least two thirds by active secretion and having a biological half-life of 1 hr. To maintain therapeutic range, the drug should be administered 3-4 times a day, which leads to saw tooth kinetic and resulting in ineffective therapy[5]. The tablet should release 125 mg of cephalexin initially within first 1 h and 46.7 mg of cephalexin per hour for next 5 h from 375 mg of total dose in order to maintain plasma cephalexin concentration of 4.5 mg/l. The percentage of drug to be released from an ideal tablet containing 375 mg of cephalexin[6].

The objective of my study to develop a Hydroxypropyl methylcellulose (HPMC 15cps) based cephalexin

extended release tablet, which can release the drug for six hours at predetermined rate and evaluate different formulation parameters like bulk density, tapped density, compressibility index, Hausner ration, tablet hardness, friability, uniformity of weight, uniformity of drug content and stability study.

Material and Methods

Materials

Cephalexin was received as a gift sample from Ranbaxy Lab. Ltd., Dewas. Hydroxypropyl methylcellulose (HPMC 15cps), Microcrystalline cellulose and Magnesium Stearate were gifted from Aura Nutraceuticals Ltd., Budasan, Gujarat.

Preparation of cephalexin extended release tablets by direct compression method[7]

Cephalexin extended release tablets were prepared by direct compression method. Tablets each containing 375 mg cephalexin was prepared as per formula given in table 1. The drug and all excipients except lubricant were passed through sieve 40# and mixed manually for 10 min. Magnesium stearate were passed through sieve 60#. Finally all the materials were mixed thoroughly. Microcrystalline cellulose was used as a directly compressible vehicle. Hydroxypropyl Methylcellulose (HPMC 15 cps) was used in different ratios as a polymer. The powder was compressed using cadmach compression machine equipped with 16/32 flat punches having break line on one side by direct compression technique.

Physical Evaluation of Cephalexin Powder Blend

Bulk density and Tapped density of the powder blend was determined with graduated cylinders according to USP guidelines. Angle of repose, Haunser's ratio and Carr's index was determined to assess the flow property and compressibility of the powder blend.

Evaluation of Cephalexin Extended Release Tablets

Weight variation test[8]

Weight variation test was done by weighing 20 tablets individually, by using Sartorious balance (Model CP-224 S). Calculating the average weight and comparing the individual tablet weight to the average weight.

Tablet thickness[8]

The thickness was measured by placing tablet between two arms of the Varnier calipers. 5 tablets were taken and their thickness was measured.

Tablet hardness[8]

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Tablet friability[8]

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ Friability} = \frac{W_0 - W}{W_0} \times 100$$

Drug content[6]

Twenty tablets were weighed and powdered. The quantity equivalent to 100 mg of cephalexin was weighed accurately and taken in 100 ml volumetric flask. Fifty milliliters of PBS pH 7.4 was added, mix for 5 min, made up to 100 ml with PBS pH 7.4, and filtered. Two milliliters of above solution was diluted to 100 ml in a volumetric flask and the drug determined at 261 nm by using UV-visible spectrophotometer.

In- Vitro dissolution studies[6]

In vitro dissolution studies of Cephalexin were carried out in 0.1 N HCl for 1 h, and continued in 0.01N HCl for another 1 h and finally in phosphate buffer pH 7.4 for 4 hours. The studies were performed in USP apparatus 1 (Electrolab), at 37±2ºC and 100 rpm. Samples were taken at hourly interval and analyzed for cephalexin content at 261 nm by using UV-Visible spectrophotometer.

Stability study[6]

The formulated cephalexin tablets, formulation F-5, which gave *in-vitro* drug release in predetermined rate, were kept for a short term accelerated stability study in stability chamber at 40±2 ºC/75±5% RH for three months as per "International Conference on Harmonization states" (ICH) guidelines. Samples were withdrawn for every month of storage and evaluated for appearance, hardness, Uniformity of weight, Friability and drug content.

Results and Conclusion

In this study, Six Formulations of cephalexin extended release tablets were prepared using HPMC 15cps (as per the formula given in table 1) in lower to higher concentration with respect to drug, which could release the drug in predetermined rate for 6 hours by direct compression method. Tablets were evaluated for physical properties, Thickness, Hardness, Friability, Weight variation, Drug content uniformity, *In vitro* dissolution study was carried on USP dissolution apparatus 1 and stability studies.

The results of angle of repose and compressibility index (%) ranged from (24.15±0.01to 29.17±0.02) and (16.45±0.02to 20.47±0.02), respectively. The results of loose bulk density and tapped bulk density ranged from (0.64±0.02gm/cm^3 to 0.66±0.02gm/cm^3) and

(0.78±0.01gm/cm^3 to 0.80±0.02gm/cm^3), respectively. The results of angle of repose (<30) and compressibility index indicates good flow properties of powder blend (Table 2).

The physical properties of different batches of extended release tablets are given in (Table 3). Tablet mean thickness was almost uniform in all the formulations. The thickness varies between 2.9±0.05 to 3.8±0.02 mm. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 7.54±0.01 kg/cm^2 to 10.24±0.03 kg/cm^2. Friability values below 1% were an indication of good mechanical resistance of the tablets. All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weight variation in all the six formulations was found to be 443±1.52 mg to 450.0±3.60 mg. The percentage drug content of all the tablets was found to be between 97.18%±0.48 to 99.78%±0.07 of cephalexin which was within the acceptable limits.

The dissolution rate profile of all the six formulations showed that a higher amount of HPMC 15cps in tablet composition resulted in reduced drug release. Formulation F-5 having a composition of 13.3% HPMC 15cps gave a predetermined release for 6 hrs from all the other formulation F-1, F-2, F-3, F-4 and F-6. So it was concluded that formulation F-5 is an optimized batch because its drug release profile (fig. 1) shows drug release for six hours in predetermined rate. At higher percentage of HPMC in tablets, when in contact with release medium, HPMC may swell and form a thick gel, thus may decrease the size of the pores present in the tablet and reducing the drug release.

Formulation F-5 which showed promising results, were subjected to stability studies at ambient room conditions for 3 months. After 3 months, extended release tablets did not show any change in physical appearance or drug content. In the formulation using HPMC 15cps polymer with the concentration of 13.3% and hardness 10.24±0.02 kg/cm^2, Percentage friability and % drug content were found 0.5326%±0.01 and 90.76%±0.10, respectively and were within the acceptable limit.

Cephalexin extended release tablets were prepared by direct compression method. HPMC 15cps polymer from lower to higher concentration was used with respect to drug. It was concluded that the formulation F-5 containing HPMC 15cps 13.3% with respect to drug gives drug release in six hours at predetermined rate from all the other formulation F-1, F-2, F-3, F-4, and F-6. As we increase the HPMC 15cps concentration the drug release get decreased. So the formulation F-5 was selected as an optimum formulation. And in stability testing of batch F-5, tablets did not show any change in physical appearance, drug content and drug release profile.

Table 1: Composition of extended release tablets of cephalexin

Ingredients	Formulation Code (in mg)					
	F1	F2	F3	F4	F5	F6
Cephalexin	375	375	375	375	375	375
Hydroxypropyl Methylcellulose (HPMC) 15 cps	20	27.4	35	42.4	50	57.3
Microcrystalline cellulose Powder	45	37.6	30	22.6	15	7.7
Magnesium sterate	5	5	5	5	5	5
Total	445	445	445	445	445	445
% of HPMC 15cps to cephalexin	5.3	7.3	9.3	11.3	13.3	15.3

Table 2: Preformulation studies

Each represents mean ± SD (n=3)

FC	Angle of Repose (θ)	Loose Bulk Density (gm/cm^3)	Tapped Bulk Density (gm/cm^3)	Hausner's ratio	Carr's Compressibility index
F1	29.17±0.02	0.64±0.02	0.80±0.02	1.25±0.02	20.47±0.02
F2	28.23±0.01	0.63±0.04	0.78±0.01	1.23±0.03	19.07±0.02
F3	27.31±0.03	0.64±0.02	0.79±0.03	1.23±0.03	19.26±0.01
F4	25.22±0.03	0.65±0.03	0.79±0.02	1.20±0.02	16.83±0.03
F5	26.22±0.02	0.66±0.02	0.79±0.01	1.19±0.04	16.45±0.02
F6	24.15±0.01	0.65±0.01	0.78±0.04	1.20±0.02	16.66±0.01

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Table 3: Evaluation parameters of cephalexin extended release tablets

FC	Parameters				
	Thickness (mm)	Average weight (mg)	Hardness (kg/cm^2)	% Friability	% drug content
F1	3.83±0.02	446±2.30	7.54±0.01	0.3633±0.01	97.18±0.48
F2	3.67±0.03	443±1.52	8.39±0.02	0.2103±0.04	98.32±0.10
F3	3.28±0.03	450±3.60	9.70±0.01	0.1496±0.03	97.54±0.40
F4	3.19±0.02	445±1.15	10.16±0.04	0.1356±0.01	99.78±0.07
F5	2.98±0.03	448±1.52	10.24±0.03	0.1035±0.04	98.86±0.05
F6	2.90±0.05	446±0.57	10.35±0.06	0.1022±0.02	97.35±0.02

Each represents mean ± SD (n=3)

Table 4: Stability study of optimized cephalexin extended release tablets

Stability duration (Days)	Appearance	Hardness (kg/cm^2)	Uniformity of weight (mg)	Friability (%)	Drug content (%)
Initial	White	10.24±0.02	448±1.53	0.1035±0.04	98.86±0.41
After 30	White	9.56±0.06	448±1.57	0.3921±0.01	95.67±0.03
After 60	White	9.12±0.01	448±2.30	0.4351±0.03	92.45±0.07
After 90	White	7.51±0.03	446±3.60	0.5326±0.01	90.76±0.10

Each represents mean ± SD (n=3)

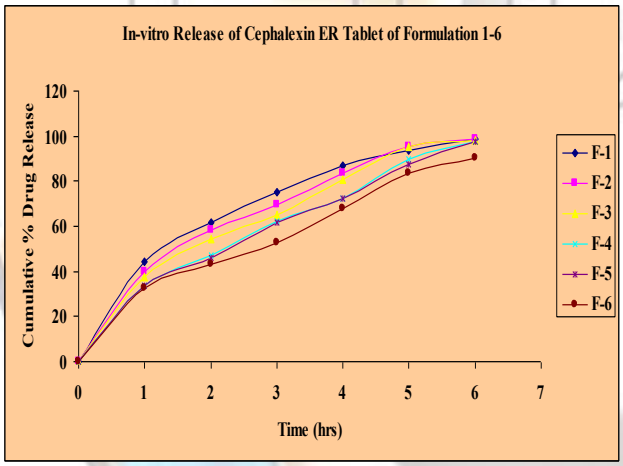

Fig. 1: *In-Vitro* release of cephalexin extended release tablet of formulation F1 to F6

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