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DESIGN AND EVALUATION OF MINI TABLET IN CAPSULE FORMULATION OF CHOLINE FINIFIBRATE

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ABSTRACT

To improve the half-life and bioavailability we have designed twice daily mini-tablets formulation of cholin feno fibrate. The system comprises of 6 matrix mini-tablets weighing 25 mg encapsulated in HPMC capsule (size1). For achieving the sustain releaseprofile, various viscosity grades of Hydroxy propyl methyl cellulose polymer (HPMC K4M, K15M, K100M) were used. The mini -tablets werepreprared by direct-compression method. The prepared mini-tablets were subjected for pre-compressional and post-compressional parameters. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. All the postcompressionalparameter evaluated were within acceptable limits. The *in-vitro* performance of our best mini-tablets formulation showed the desired behavior, nearly 99.57 % of drug was sustained for a period of 12 hrs.

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INTRODUCTION

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs through different drug delivery systems such as tablets, injectables, suspensions, creams, ointments, liquids and aerosols. The delivery systems is to allow the safe application of the drug. This includes that the drug in the formulation must be chemically, physically and microbiologically stable.[1] This means the pharmaceutical quality of the delivery systems needs to be assured, drug release from the system needs to be reproducible and the influence of the body on drug release should be minimized. [2] The ultimate goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration.

Mini-tablets are small tablets with a diameter typically equal to or less than 3 mm that are typically filled into a capsule, or occasionally, further compressed into larger tablets. It is possible to incorporate many different mini-tablets, each one formulated individually and programmed to release drug at different sites within the gastrointestinal track, into one capsule. These combinations may include immediate release, delayed release, and/or controlled release mini-tablets. It is also possible to incorporate mini-tablets of different drugs to treat concurrent diseases or combinations of drugs to improve overall therapeutic outcome, while delivering distinct release rates of each according to disease requirements (4,5)

Choline Fenofibrate is BCS class I drug which has good water solubility. Bioavailability of Choline Fenofibrate is solely dependent on the dissolution rate, absorption of drug through gastro intestinal tract. (6,7)

The main aim of the present work is to develop delayed extended release Choline Fenofibrate capsules, which is a highly protein binding drug in order to meet the required bio-availability and to study the *in-vitro* release pattern.

MATERIALS

choline fenifibrate was received as a gift sample from Hetero drugs pvt ltd, Hyderabad. HPMC different grade, HPMC K4M, HPMC K 15M eudragit, and HPMC K 100M procured from SD fine chemiclas, and polishing agent are microcrystalline cellulose, Povidone and diethyl phthalate. These all polymers are used in different ratios for different formulations. Isopropyl alcohol is used as solvent were obtained from sigma Aldrich pvt ltd.

EXPERIMENTAL

Preparation of mini tablets of choline finifibrate

Mini tablets of choline fenifibrate were prepared by using various viscosity grades of polymers (HPMC K4M, HPMC K 15M eudragit, and HPMC K 100M)as matrix forming material. All ingredients (Drug polymer, PVP K-30, Avicel,) were passed through a #100 sieve, weighed, and blended. The lubricated formulations were compressed by a direct compression technique,using using 3 mm flat round convex punches in a rotary tablet press(Rimek mini press, model RSB-4, M/S: Karnavathi engineering,Ahmadabad). Six mini tablets containing each 176.68 mg of choloine finofibrate was filled in to 1-size empty hard gelatin capsule.

EVALUATION:

a. Bulk Density

Bulk density was determined by USP method-I. 20g of blend were taken and poured into a measuring cylinder. Bulk volume of blend was noted and the bulk density was calculated by the following formula.

Bulk density= Mass of blend/ Bulk Volume.

b. Tap Density:

Tap Density was determined with tap density tester, by placing a graduated cylinder containing a 20g of blend in it, which was then operated for 500 taps and the tapped density was calculated by the following formula.

Tapped density= Mass of blend/ Tapped Volume.

c. Compressibility Index :

It is an important measure that was obtained from the bulk and tapped densities. In theory, the less compressible a material the flow able it is. A material having values of less than 20-30% is defined as the free flowing material. It was calculated for all the formulations.

CI=TBD-LBD/TBD*100

Where,

TBD=Tapped bulk density

LBD=Loose bulk density.

d.Hausner's Ratio:

It indicates the flow properties of powder and was measured by the ratio of tapped density to bulk density.

Hausner's ratio=Tapped density/Bulk density

Both the compressibility index and the Hausner ratio were determined by using bulk density and the tapped density of a powder.

Evaluation Tests for coated minitablets[12]

- **a.** Weight variation
- **b.** Hardness
- **c.** Thickness
- **d.** Diameter

1. Weight Variation Test: 20 intact capsules were selected randomly and weighed and average weight was calculated. Individual weight of each capsule was determined. According to USP, none of the individual capsule weight should be less than 90% and more than 110% of the average weight.

2. Hardness: The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm2. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

3. Thickness: The thickness of ten randomly selected core/coated tablets from each batch was individually recorded in mm using a digital caliper (Mitutoyo digimatic caliper, Mitutoyo Corporation, Japan) and screw gauge. The mean and standard deviation values were calculated from each value recorded.

4. Friability (F) : A friability test was conducted on the mini-tablets using a veego friabilator. Twenty mini-tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The mini-tablets were initially weighed (Winitial) and transferred into friabilator. The drum was rotated at 25 rpm for 4 minutes after which the mini-tablets were removed. Any loose dust was removed from the mini-tablets as before and the tablets were weighed again (Wfinal).

EVALUATION OF CAPSULE

a. Weight Variation Test:

20 intact capsules were selected randomly and weighed and average weight was calculated. Individual weight of each capsule was determined. According to USP, none of the individual capsule weight should be less than 90% and more than 110% of the average weight.

b. *In vitro* dissolution studies:

In vitro drug release studies were carried out using a USP type II dissolution test apparatus at 100 rpm for 2 hr in 3.5 Ph phosphate buffer (500 ml) maintained at 37°C ± 0.5°C and 10 ml of sample was withdrawn and analyzed using UV spectrophotometer at 286 nm.

Then, the dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and tested for drug release for 6 hr at same temperature and same rotation speed. At all the time points 15, 30, 60, 90, 120, 240 and 360 minutes, 10 ml of the samples were withdrawn, and analyzed using UV spectrophotometer 286 nm.

RESULTS AND DISCUSSION

The mini tablets of choline fenofibrate and after filling the capsules were evaluated for pre formulation parameters

FLOW PROPERTIES (pre compression parameters)

s.no.	Formulation code	Tapped density(gm/ml)	Bulk density (gm/ml)	Compressibility index (%)	Hausner's ratio
1.	F1	0.741	0.527	28.87	1.40
2.	F2	0.506	0.437	13.63	1.15
3.	F3	0.642	0.58	22.11	1.29
4.	F4	0.671	0.52	22.5	1.29
5.	F5	0.653	0.53	18.83	1.23
6.	F6	0.661	0.51	22.84	1.29
7.	F7	0.672	0.52	22.61	1.28

***Table 2* pre compression parameters of mini tablets**

The flow properties and other derived properties evaluated for all the formulations are proved to be within the limits The values for angle of repose were found in the range of

25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.64 to 0.74(gm/cc) and 0.43 to 0.58 (gm/cc) respectively. The Hausner ration fall in range of 1.12 to 1.29. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

POST COMPRESSION PARAMETERS OF COATED MINI TABLETS

Formulation code	Weight	Thickness	Diameter	Hardness
F1	29±1	5	3±0.1	4±0.1
F2	30±1	3	3.1±0.1	5
F3	29±2	3	3±0.2	6
F4	31±1	3.2	3.2±0.1	5.5
F5	30±1	3	3.1±0.2	4
F6	28±2	3	3±0.1	5
F7	29±1	3	3.1±0.1	5

The miniTablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 7.3. The average weight of the tablet is approximately in range of 29 to 31.5, so the permissible limit is ±10%.The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Weight variation of capsules filled with minitablets

Formulations	Average Weight (mg)
F1	370.1 ± 3.6
F2	371.2 ± 5.8
F3	370.7 ± 4.5
F4	372.5 ± 3.5
F5	371.6 ± 3.2
F6	372.3 ± 4.5
F7	370.1 ± 4.6

Table-3 Weight variation of capsules filled with minitablets

Each batch of minitablets were filled in to the capsule and were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table-3. The average weight of the tablet is approximately in range of 360 to 372.5, so the permissible limit is ±10%.The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 3. The results showed that the hardness of the tablets is in range of 4 to 5.5 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-7.3 The result showed that thickness of the tablet is raging from 3.06 to 3.14.

***In-Vitro* Drug Release Profile:**

Dissolution by UV:

Medium : 3.5pH sodium phosphate buffer

Volume : 500ml

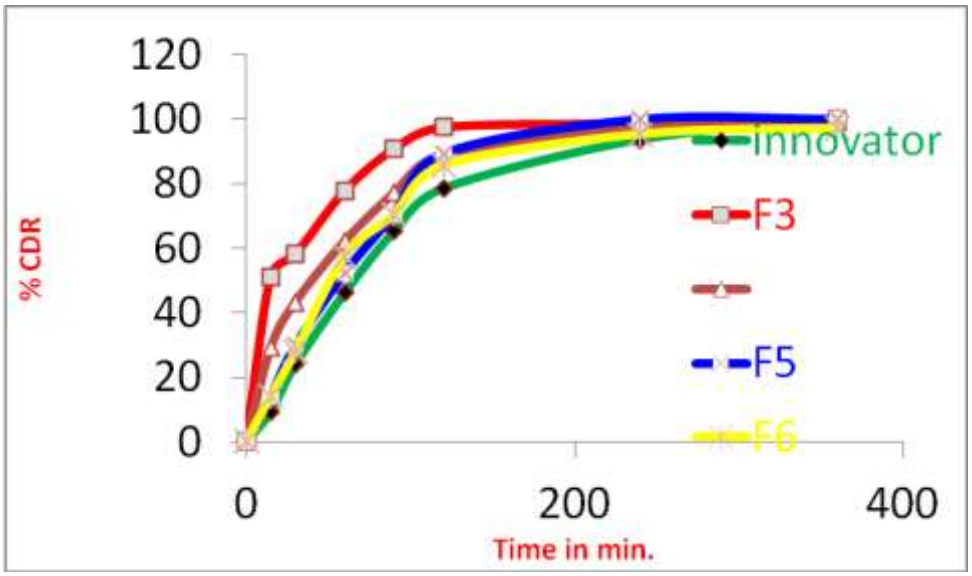
Apparatus : Paddle (II)

RPM : 50

Time Points : 2 hrs.

Temperature : 37±0.5°C

followed by dissolution in 900ml of 6.8 pH phosphate buffer in USP Apparatus 2, at speed of 50 rpm, and a temperature of 37±0.5°c, for 360 minutes.



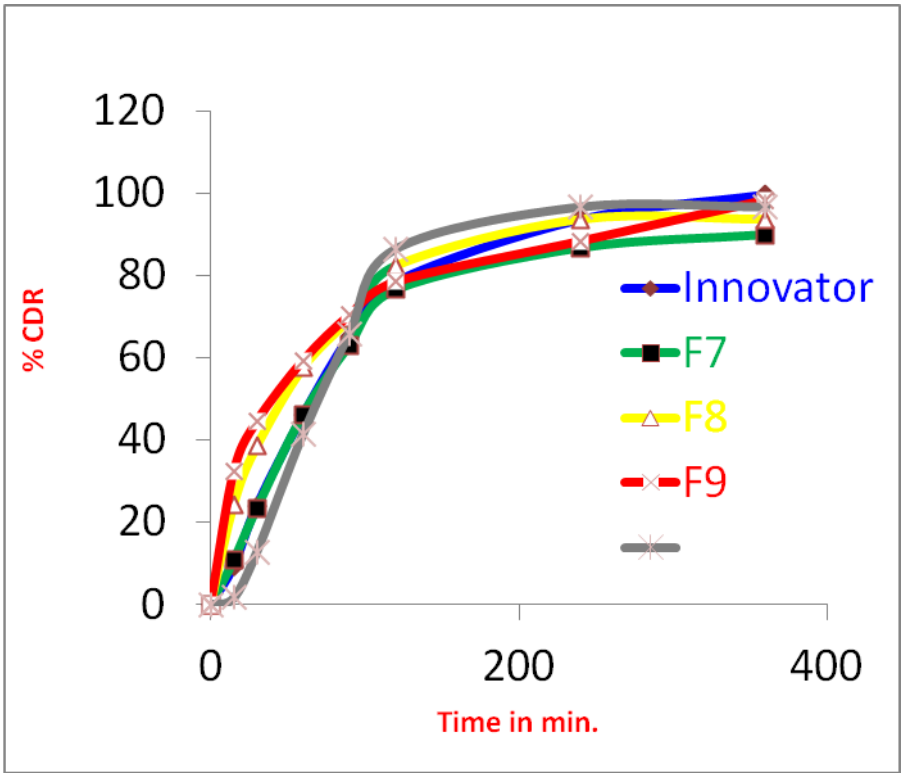


Figure-1 Dissolution profile of choline fenofibrate capsules

The Dissolution profile of choline fenofibrate capsules was conducted in phosphate buffer showed sustained release for prolonge period. The release was similar to innovator. The drug release was found to be more than 50 percentage after 120 min.

Based on the pre formulation parameters and dissolution profile F4 formulation was selected as a optimized formulation

Conclusion

The present work is to develop delayed extended release Choline Fenofibrate capsules meet the requirements of formulation development

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