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Formulation and characterization of choline fenofibrate sustained release capsule

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ABSTRACT

The drug ABT-335 (Fenofibricacid) choline fenofibrate found to be useful in the treatment of dyslipidemia as compare with other fibrate. So the present investigation to developed mini-tablets to overcome the dose dumping problem by regular shape, uniformity, smooth surface excellent size and encapsulated in capsule to improve the efficacy and bioavailability of the drug. Different formulations were developed by utilizingcontrolling of the release rate and gel forming polymers like microcrystalline cellulose, hypromellose by dry granulation technique. Among all formulation SRM-3 having the drug release for longer period of time as compare to other formulation. SRM-3 was found to be stable during stability study for one month.

Keywords: ABT-335 (Fenofibric acid) choline fenofibrate, like microcrystalline cellulose, hypromellose, sustained release matrix tablet.

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INTRODUCTION

Controlled drug delivery technology suggests a quantitative comprehension of physicochemical mechanism of availability of drug to the sustained that dosage form release rate can be determined.Promising development and new strategy to oral controlled release drug delivery includes hydrodynamic pressure controlled system.The oral administration is considered because of its convenience of self-administration, compactness and easy manufacturing.[1,2]For controlled–release system, oral route of drug administration has attracted most attention. This is because there is more flexibility of dosing.

The high level of cholesterol in the blood can raise a personchances for developing heart disease. Cholesterol has transported to the blood stream by carrier proteins known as lipoproteins. Low density lipoproteins (LDL) tend to deposit cholesterol-laden "plaques' in artery walls, narrowing the opening through which blood flows and increasing the risk of heart disease. The LDL cholesterol has been dubbed the "Bed" cholesterol and high density lipoproteins (HDL) cholesterol is known as "good" cholesterol because HDL carries cholesterol to the liver. It is breakdown and remove from the blood it can wind upon artery walls. High blood level triglycerides, the body's storage from of fat and a primary source of energy, are also associated with a great risk of heart disease.[3-5]

Various synthetic preparations are available for dislipidemia like HMG-COA reductase inhibitors (statins), fibric acid derivatives (fibrates), clofibrate, gemfibrozil, tricor, lofibra. These conventional tablets are associated with an increased incidence of gallstones, myopathy, rhabdomyolysis, destruction of muscular tissue, gastrointestinal disturbances, headache, abdominal pain nausea, vomiting, constipation. Due to this, powerful strain drug, cerivastin (lipobay) and clofibrate was withdrawn because of this complication. To overcome the drawback of older fibrate to design the new ABT-335 (fenofibric acid) Choline fenofibrate sustained release tablet, particularly interm of pharmacokinetic properties. Which does not needed enzymatic cleavage to become active. It easily dissociates to active from free fenofibric acid and does not undergo fast pass hepatic metabolism. The fenofibric acid is well absorbed through out GIT and statistically increased bioavailability then other fibrate.

The drug ABT-335 (fenofibric acid) choline fenofibrate found to be useful in the treatment of dyslipidaemia as compared with other fibrates. For controlled drug delivery system, oral route of administration has attracted most attention. This is

because there is more flexibility of dosing. The design of the matrix tablet to overcome the problem of dose dumping by excellent size uniformity, shape and smooth surface and this also improve the bioavailability and efficacy of the drug.

MATERIALS AND METHODS

Choline fenofibrate was obtained as gift sample from Aristo pharmaceutical, Bhopal, M.P, India. Microcrystalline cellulose, Hypromellose, polyvinaylpyrolidone, colloidal silicon dioxide and Sodium stearyl fumarate were procured from Aristo Pharmaceutical pvt Ltd, Bhopal, M.P, India.. All other chemicals and ingredients used for study were of analytical grade.

Preparation of Sustained Release Matrix Tablet:

Choline fenofibrate, Hypromelloseand microcrystalline cellulose through sieve 30 and mix properly.Take 20 ml of purified water in a beaker and add polyvinyl pyrolidone to it under stirring to dissolve. Granulate the contents of step 1 with binder solution of step 2 in a stainless still bowl. Dry the wet mass in a rapid dryer with an inlet temperature of 50-55^{0}Cfor 10-15 minutes. Pass the dried granules through sieve no20 and collect in a tight container. Pass the colloidal silicon dioxide through sieve no 40 and mix with dried granules for 3 minutes. Pass sodium stearyl fumarate through sieve no 60 and mix with sample. Compress the blend using 2.90mm multi-tip punch standard concave and plain on both side and note the parameters.[6]

Table 1: Formulation of Choline Fenofibrate Matrix Tablet

Ingradients	Formulations		
	SRM1	SRM 2	SRM 3
Choline fenofibrate	178.83	178.83	178.83
Microcrystalline cellulose	75.26	62.57	54.99
Hypromellose	10.0	20.0	30.0
Polyvinyl pyrolidone	2.69	2.69	2.69
Colloidal silicon dioxide	0.53	0.53	0.53
Sodium lauryl fumarate	2.69	5.38	5.38

Characterization of Sustained Release Tablet:

The granulation blends of sustained release tablet are compressed into tablets by using 2.90mm multi-tip punch standard concave and plain on both sides on a tablet machine (SHIMO Machinary). All batches are prepared tablets were evaluated employing following parameter like weight variation, hardness, friability test and drug content.

Weight Variation:[7]

Twenty tablets were individually weighed and then their average weight was calculated. The average weight was com[pared with the individual tablets weight and the weight variation was calculated. The weight of a tablet should be within acceptable limits as it is an important property that influence the amount of drug present in it.

Hardness:[7]

The tablet requiredcertain amount of strength of hardness and resistance to friability, to withstand mechanical shocks while handling, packaging or transportation. The hardness of the prepared tablet was determined by using Monsanto hardness tester. For each batch five tablets were tested and average was calculated.

Friability:[7]

The tablet were weighted and introduced into friability apparatus (Electrolab) the apparatus was operated for 100 revolutions. The tablets were then removed, dusted and percentage friability was calculated using following formula

% friability = {1-(Wt -/W)} × 100

Where, W = Initial weight of tablets

Wt = Weight of tablets after 100 revolution.

Drug content:[8]

Content of 10 capsules (120 tablets) were weighted and finely powdered, accurately powder of 12 tablets, transferred in a 10 ml volumetric flask and dissolve in 10 ml phosphate buffer and filtered it and observed the reading in UV. The results were mentioned in the table.

Dissolution Study:[9, 10-11]

A single capsule was placed in a vessel. Fastened to the bottom of the shift. Connected to a variable speed of motors. The vessels were filled with the dissolution medium (6.8 phosphate buffer) and the temperature were maintained at 37 ±0.5 ^{C} using a constant temperature bath.The shaft is adjusted to turn at the specified speed and the sample of the fluid are withdrawn at intervals to determine the amount of drug in solution. At same time add equal amount of fresh medium into the dissolution vessels.

RESULTS AND DISCUSSION

Charecterization of sustained release tablet:

Various micromeritics properties were performed on bland. The angle of repose was found to be 34^0, tapped density was 0.57, bulk density was 0.46, compressibility index was 13.72, Hausner's ratio was 1.15. All parameter was found to be in range. The formulation sustained release matrix tablet was optimized by trial and error method. Three batches were designed by using different amount of hyoermellose and sodium steryll fumarate to overcome the problem of sticking. The tablets were prepared and characterised.

Micrimeritics properties are given below:

Table 2: Micromeritics properties of choline fenofibrate

Parameter	Parameter		
	SRM-01	SRM-02	SRM-03
Bulk Density	0.462	0.44	0.46
Tapped Density	0.57	0.56	0.57
Compressibility Index (%)	15.09	13.20	13.72
Hausners ratio	1.16	1.15	1.15
Loss on drying	3.11	3.10	3.11
Angle of repose	31	33	34

All the formulations were evaluated for weight variation, hardness, thickness, friability and % drug content. The tablets tested were found to have acceptable limit (±55%) of weight variation and therefore passes the test. The results were recorded in table. The hardness was to be found to be within the design input values as desired i.e. 5kg/cm^2. The results are recorded in table 2. The friability of tablets was found to be within acceptable limits, i.e. less than 1% as specified USP.

Table 3: Characterization of formulated sustained release tablet of choline fenofibrate

Formulation Code	Weight (mg)	% weight variation	Hardness (Kps)	Friability (%)	Drug Content (%)
SRM-01	22.62	1.90	3.2	0.46	98.29
SRM-02	22.54	1.64	2.8	0.32	97.82
SRM-03	22.6	1.98	3.0	0.54	99.29

The formulated sustained release tablets passed the weight variation and friability tests and the variations were within the permitted limits.

The release profile was observed in 6.8 phosphate buffer. The excellent release profile was found in the batch SRM-03, in which hypromellose and sodium steryl fumarate in a higher amount as compare to other batches. It was found that the developed product was not only long acting but safe effective as well.

Table 4: Correlation between dissolution data of all three batches

Time (hr)	Cumulative % drug release		
	SRM-01	SRM-02	SRM-03
1	13.86±1.73	20.30±2.55	21.83±0.55
2	26.05±1.22	35.15±3.99	38.64±0.63
4	45.52±1.37	57.914±2.44	76.80±0.93
6	58.50±1.79	68.48±1.53	90.84±0.65
8	68.61±1.33	77.26±2.81	95.37±0.97
10	91.08±1.95	96.00±2.40	96.70±0.49
12	95.40±1.77	96.06±3.42	98.07±0.57

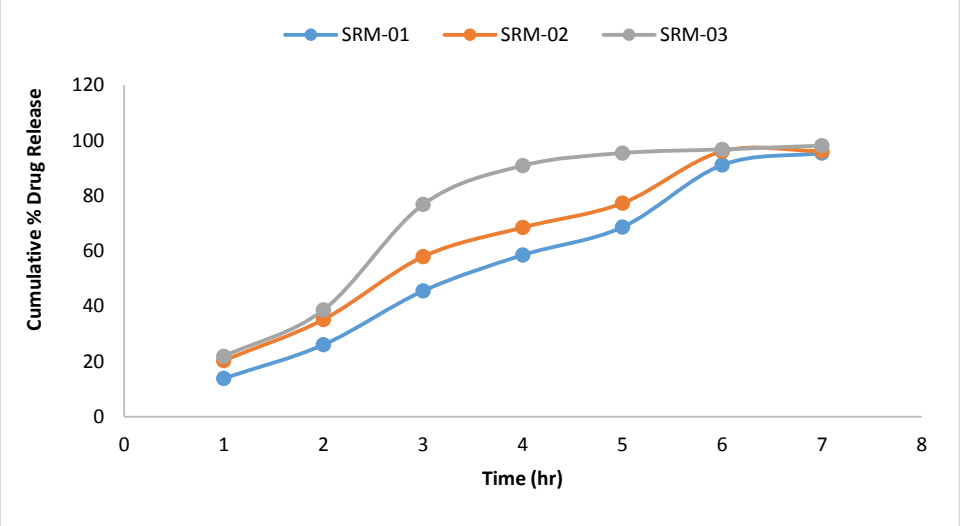

Figure 1: Drug Release profile of Matrix tablet

Among all three dissolution data, the dissolution data of SRM-03 was found to be excellent release profile (98%) as compared to the other two batches (SRM-01 & SRM-02).In which hypromellose and sodium stearyl fumarate in a higher as compare to other batches. It was found that the developed product was not only long acting but safe and effective as well.

Stability studies were carried out of the most satisfactory formulation F1, at 30 ± 2°C / 65 ± 5% RH and 40 ± 2°C / 75 ± 5% RH for two months to assess their long term stability as per ICH guidelines. At various time intervals of 30 days and 60 days, samples were evaluated. There was no major change in the various physicochemical parameters evaluated like hardness, drug content, *in-vitro* dissolution pattern at the various sampling points. There was no statistically significant difference between the initial values and the results obtained during stability study.

CONCLUSION

Fibrates are used to relieve from the hyperlipidemia by reducing the cholesterol level. In the present study it was developed a sustained release matrix delivery of ABT-335 (Fenofibric acid) choline Fenofibrate, which has high capacity of lipolysis and elimination of triglycerides rich particle from plasma. SRM-03 was found to be excellent release profile (98%) as compared to the other two batches (SRM-01 & SRM-02). In which hypromellose and sodium stearyl fumarate in a higher as compare to other batches.

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