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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLET OF ATORVASTATIN CALCIUM

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ABSTRACT

Most of the orally administered dosage forms have several physiological limitations, such as GI transit time, impaired drug absorption due to incomplete release of drug from the dosage forms and too short residence time of the dosage forms in the absorption region of GI tract. Gastro Retentive Drug Delivery Systems (GRDDS) offer a promising approach to address these challenges, particularly for drugs like Atorvastatin calcium, which undergo rapid clearance in the intestine. Atorvastatin Calcium is a HMG-CoA reductase inhibitor used in treatment of hyperlipidemia. It undergoes high first pass metabolism. It is absorbed more in the upper part of the GIT. In This investigation describes the preparation and evaluation of gastro retentive floating tablets of atorvastatin calcium. One hydrophilic cellulose derivative, Methocel K4M were used in floating tablets as gel forming agents to control drug release. Sodium bicarbonate was incorporated as gas generating agents. The tablets prepared by direct compression technique were evaluated by various quality parameters including physical parameters, weight variation, hardness and Content uniformity.

KEYWORDS: Gastro Retentive Drug Delivery, Atorvastatin calcium, Floating Tablet, HMG-CoA reductase.

1. INTRODUCTION

The development of controlled-release formulations continues to be a big success for the pharmaceutical industry. The success of any technology relies on the ease of its manufacturing process and its reproducibility of desirable biopharmaceutical properties.

Amongst all of the above controlled drug delivery systems, oral controlled release delivery has received major attention because of its greater popularity, and it provide a uniform concentration/amount of drug at the absorption site and thus after absorption, allow maintenance of plasma concentration with in therapeutic range, which minimizes side effects and also reduces the frequency of administration.[1]

"Oral controlled drug delivery systems are those that provide continuous oral delivery of drugs at predictable and reproducible kinetics, for a predetermined period throughout the course of GI transit".[2]

1.1 Gastro intestinal retention controlled drug delivery system[3]

Among the different type of formulation, gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Gastro Retentive drug delivery systems can be retained in the stomach for a long time. Such retention systems are important for drugs that are degraded in intestine or for drugs like antacids or certain antibiotics. The main objective of developing these systems is to increase the safety of a product, to extend its duration of action and decrease the side effects of drugs.

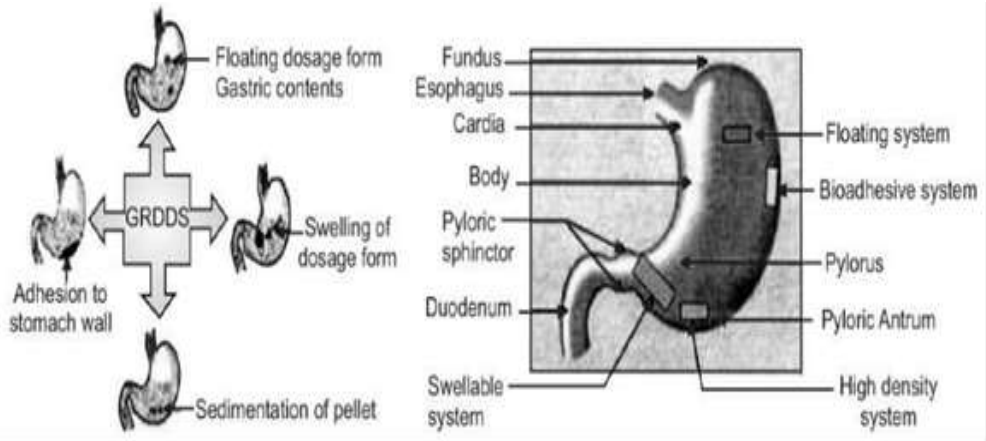

Fig. no. 1: Approaches of gastro retentive drug delivery system.

1.2 Floating drug delivering system

These are systems which have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of

time. While the system is floating on the gastric contents, the drug is released slowly at desired rate from the system. Based on the mechanism of buoyancy, FDDS are classified into two distinctly different technologies, i.e., Non-effervescent and Effervescent systems.

- ✓ **Non-Effervescent floating dosage forms:** Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of less than 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

- ✓ **Effervescent floating dosage forms:** These are matrix types of systems prepared with the help of swellable polymers such a as methylcellulose and chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

1.3 Advantages of floating drug delivery systems[4]

- ✓ **Sustained drug delivery:** These systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time, encountered with an oral CR formulation can hence be overcome with these systems. These systems have a bulk density of < 1, as a result of which they can float on the gastric contents.

- ✓ **Site-Specific drug delivery:** These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. Eg. Riboflavin, Furosemide, Ciprofloxacin, etc.

- ✓ **Absorption enhancement:** Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

1.4 Atorvastatin calcium

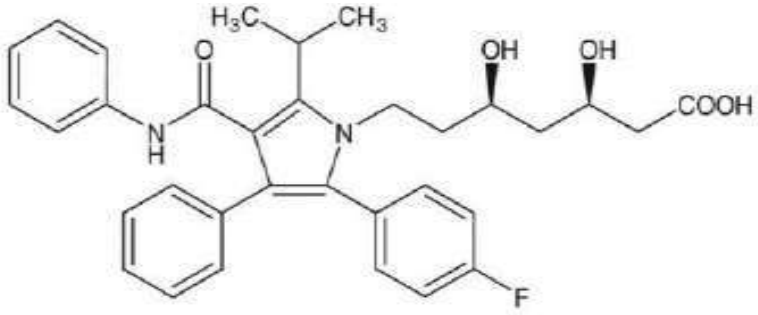

Fig. no. 2: Structure of atorvastatin.

Table no. 1: Physical properties of atorvastatin calcium.

Synonyms	➢ Atorvastatin calcium trihydrate ➢ Totalip ➢ Atorvastatin calcium ➢ Torvast ➢ Atorvastatin hemicalcium trihydrate ➢ Atorvastatin calcium [usan]
IUPAC name	(3R,5R)-7-[2-(4-Fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid
Appearance	White to off-white crystalline powder.
Molecular Formula	$C_{66}H_{74}CaF_2N_4O_{13}$
Molecular Weight	1209.4 g/mol
Melting Point	176 **°c**
Boiling Point	722 **°c**
Solubility	**Freely soluble:** methanol; **Slightly soluble:** ethanol; **Very slightly soluble:** acetonitrile, distilled water

2. MATERIAL AND METHODS

Material

In this work all reagents and excipients were used have analytical grade. Atorvastatin Calcium received a gift sample from Piramal Pharma Limited, Pithampur. Excipients such as HPMC, Guar Gum and Lactose from Milton Chemicals, Mumbai, India, Magnesium Stearate and Talc from Sunchem, India and Sodium bicarbonate from Loba Chemie.

Method

The active ingredient and other excipients were accurately weighed according to the formulations (Table 2). Particular attention was given to ensure uniform mixing of the components. The mixture was accurately weighed in an electronic balance (Model: AY-200, SHIMADZU Corporation, Japan) for the preparation of each tablet and finally compressed by

using a laboratory hydraulic press. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight containers at room temperature for further study.

Preparation of floating tablets by direct compression method: Floating tablets were prepared by direct compression method using variable concentrations of HPMC, Guar Gum. Sift the Atorvastatin calcium, HPMC, Guar Gum, Sodium bicarbonate, Lactose was sifted and passed through #40 mesh and collected in a double lined poly bag and Magnesium stearate, Talc was passed through # 60 mesh and collected it in double lined poly bag separately. Then the major raw materials were mixed with the lubricant. Lubricated blend was compressed using compression machine with average weight of 250 mg.

Table no. 2: Composition of formulation.

S. No.	Ingredients	Category	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
1	Atorvastatin Calcium	Active Ingredient	100	100	100	100
2	HPMC	Polymer	5	-	10	-
3	Methocel K4M	Gel Forming Agents	100	100	105	105
4	Guar Gum	Polymer	-	15	-	5
5	Sodium Bicarbonate	Gas Generating agent	10	15	10	12.5
6	Lactose	Diluent	20	15	15	20
7	Magnesium stearate	Lubricant	10	5	10	7.5
8	Talc	Glidant	0.5	0.5	0.5	0.5

3. Evaluation

- **Preformulation evaluation of drug**

➢ **Angle of repose**

It is defined as the maximum angle possible between the surface of the pile of the powder and horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h) above a flat horizontal surface to which a graph paper was placed. The granules were carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. It was then calculated using the formula

$\tan \theta = h/r$

Where, θ = Angle of Repose, h = Height of Pile, r = Radius of the base of the pile

➢ **Bulk density**

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantities of granules

were carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. It was expressed in gm/ml and given by *BD = Wg/Bg* Where, BD = Bulk density, Wg = Weight of granules, Bg = Bulk volume of granules.

- **Tapped density**

It is the ratio of total mass of the powder to the tapped volume of powder. The weight of sample equivalent to 10 g was filled I in 100 ml graduated cylinder. The tapping of the cylinder was carried out at a rate of 300 drops per minute for 500 times from 3" height and the tapped volume Vf was noted. The tapped density was calculated in gm/ cm3 by the formula, (ρt) = M/Vf Where, ρt– Tapped density, M = weight of sample powder taken, Vf = tapped volume.

- **Carr's consolidation index (% Compressibility):** Carr's Index explains flow properties of the granules. It is expressed in percentage and given by Consolidation Index = (Tapped Density - Untapped Density /Tapped Density) *100

- **Hausner's ratio:** Tapped density and untapped density were measured and the Hausner's ratio was calculated using the formula, Hausner's ratio = ρt/ρo, Where, ρt = tapped density; ρo = untapped density.

- **Post-Compressional evaluation**

- **Weight variation test**

Twenty tablets were weighed individually and average weight was calculated. The individual weights were then compared with average weight. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit. PD=(Wavg-Wind/Wavg)*100

where,PD = Percentage Deviation, Wavg = Average weight of tablet, Wind = Individual weight of tablet

- **Thickness and Diameter**

The thickness and diameter of the tablets were carried out using vernier caliper. Five tablets were used for the above test from each batch and results were expressed in millimetre.

➢ **Hardness**

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. Hardness was expressed in Kg/ cm2.

➢ **Friability**

Friability was determined using Roche Friabilator. Twenty tablets were weighed and placed in the friabilator and then operated at 25 rpm for four minutes. It was expressed in percentage. Friability should be < 1%. The difference in the two weights is used to calculate the friability.

Friability=100*(1-w/w0)

where, W0 = Initial weight, W = Final weight

➢ **Drug content**

Drug content was determined to check dose uniformity in the formulations. The procedure adopted for determination of drug content as initially 10 tablets were weighed and powdered. A quantity equivalent to 100 mg of Atorvastatin calcium was taken in a 100 ml volumetric flask and dissolved in small volume of methanol and made up the volume with 0.1N HCL and filtered. An aliquot of 10 ml was pipetted out into 100 ml volumetric flask and made up the volume with distilled water. Absorbance was read at 246 nm using 0.1N HCL as a blank.

4. RESULTS AND DISCUSSION

➢ **Identification of drug**

Identification of Drug by Description, Solubility and Melting Point An identification of Atorvastatin Calcium based on physical examination and melting point results are mentioned in following table.

Table no. 3: Identification of drug by Description, Solubility and Melting point.

Sr. No.	Test	Specification	Observation	Inference
1	State	Solid crystalline	Solid crystalline	Complies
2	Colour	White	White	Complies
3	Melting Point	120º C	121-125°C	Complies
4	Solubility	Freely soluble in water, soluble in methanol and sparingly soluble in ethanol	Freely soluble in water, Soluble in methanol and Sparingly soluble in ethanol	Complies

Table no. 4: Characteristics of controlled release powder blend.

Formulation	Angle of Repose	Bulk Density	Tapped Density	Hausner ratio	Carr's index
F1	20º14'±0.4649	0.350±0.011	0.410±0.006	1.17±0.003	14.63±0.680
F2	21º32'±0.6133	0.351±0.010	0.412±0.003	1.17±0.004	14.80±0.521
F3	21º17'±0.6158	0.361 0.010	0.430±0.005	1.19 ±0.002	16.20±0.180
F4	21º08'±0.4255	0.371±0.020	0.442±0.003	1.19 ±0.003	16.07±0.101

- **Evaluation of tablets**

✓ **Thickness and Diameter**

The thickness and diameter were found in the range of 2.79 ±0.016 to 2.86±0.018 and 7.0 ±0.0114 to 7.2 ±0.018 respectively.

Table no 5: Thickness and Diameter data of the tablets.

Formulation	Thickness (mm) ± S. D	Diameter(mm)± S. D
F1	2.83 ±0.013	7.1 ±0.114
F2	2.79±0.016	7.0 ±0.89
F3	2.87±0.016	7.2 ±0.018
F4	2.86 ±0.018	7.1 ±0.010

✓ **Weight Variation, Hardness and Friability**

Depending upon the ingredients of different formulations, the weight of tablet was fixed. In each formulation, weight variation was within the I.P limit. Mostly, the variation was within ± 5%. The hardness of the different formulations ranged from 5-7 kg / cm2. All the formulations exhibited less than 1% friability.

Table no. 6: Hardness, weight Variation and Friability data of the tablets.

Formulation	weight variation (mg)	Hardness (Kg/cm2)	Friability (%)
F1	152 ±1.09	5.8 ±0.244	0.31 ±0.002
F2	151±1.14	6.4 ±0.251	0.26 ±0.004
F3	150±1.14	6.3 ±0.244	0.34 ±0.003
F4	152 ±0.41	6.7 ±0.244	0.36 ±0.003

✓ **Content uniformity**

The results for content uniformity are presented in table. No. 06 The results were found to be within the limits (92 to 96.28%). It shows that the drug was uniformly distributed throughout the tablets.

Table no. 7: Content uniformity data of the tablets.

Formulation	Content uniformity (%)
F1	95.18 ± 0.11
F2	93.28 ± 0.43
F3	96.28 ± 1.00
F4	92.12 ± 1.00

5. CONCLUSION

Atorvastatin calcium is an inhibitor of 3-hydroxy-3-methylglutarylcoenzymeA (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Gastro Retentive Drug Delivery System of Atorvastatin calcium could be successfully formulated by direct compression technique, using different viscosity grades of Hydroxy Propyl Methyl Cellulose, Guar Gum was used as binder, sodium bicarbonate as gas generating agent, talc as glidant, magnesium stearate as lubricant and lactose as diluent. The optimized tablet formulation had showed 96.28% of drug release in 24 h. Therefore the optimized formulation containing HPMC with Guar gum sustained the drug release for a period of 24 h and remains buoyant throughout the studies. It is a promising approach as it can able to release the required quantity of drug to the body, which results in minimizing the major side effect as rhabdomyolysis by minimizing the drug concentration in blood and also the entire dose was released in acidic medium, where atorvastatin having more absorption and ultimately leads to better patient therapy.

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