INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN:2320-2831

IJPAR |Vol.7 | Issue 1 | Jan- Mar-2018
Journal Home page: www.ijpar.com

Research article Open Access

Formulation and evaluation of gastro retentive floating tablets of atorvastatin calcium

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ABSTRACT

Atorvastatin calcium is a HMG-CoA reductase inhibitor used in the treatment of hyperlipidaemia. Oral bioavailability of atorvastatin calcium is less than 12%. It also undergoes high first pass metabolism. It is absorbed more in the upper part of the GIT.[10] So oral absorption of atorvastatin can be increased by increasing gastric retention time of the drug. Thus it is decided to prolong the gastric residence time in terms of making floating gastro retentive drug delivery system to increase drug absorption and hence bioavailability. In this study Atorvastatin calcium floating tablets were prepared by using two different techniques like Effervescent floating tablets and Non Effervescent floating tablets using Ethyl cellulose, Karaya gum and HPMC K4 M as polymers and gas generating agents like sodium bicarbonate and citric acid and polypropylene foam powder as a selling agent in non effervescent floating tablets. The tablets prepared by direct compression technique were evaluated in terms of their pre-compression parameters and post compression characteristics such as physical characteristics, total buoyancy, buoyancy lag time, swelling index and *in vitro* release. The best formulation showed no significant change in physical appearance, drug content, total buoyancy time, buoyancy lag time or *in vitro* release after storage at 40˚C /75% RH for three months. The *in vitro* release studies confirmed that the formulation (F24) containing 90 mg of karaya gum showed sustained drug release (98.81±0.32%) for 12 h and remained buoyant for more than 12 h by using Effervescent floating technique.

INTRODUCTION

The oral route represents the predominant and most preferable route for drug delivery unlike the majority of parenteral dosage forms it allows ease of administration by the patient and highly convenient way for substances to be introduced in to the human body. Oral drug delivery systems are divided in to immediate release and modified release systems[1]. Modified release systems have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients and

patient compliance as well as reducing side effects. Oral modified release delivery systems commonly include delayed release, extended release programmed release and site specific or timed release. Oral extended release dosage forms offer the opportunity to provide constant or nearly constant drug plasma levels over an extended period of time following administration. Extended release drug delivery systems offer several advantages compared to conventional drug delivery system including avoiding drug level fluctuations by maintenance of optimum therapeutic plasma and tissue concentrations over prolonged time periods, avoiding sub therapeutic as well as toxic concentrations, thus minimizing the risk of failure of the medical treatment and undesirable side effects, reducing the administered dose and reduced frequency of administered dose while achieving comparable results, Targeting or timing of the drug action. Hence it is highly desirable to develop sustained drug delivery system releasing the drug at predetermined rates to achieve optimal plasma drug levels and/or at the site of action[2, 3].

Majority of drugs are preferentially absorbed in the upper part of the small intestine. So, Gastro retentive drug delivery systems are preferred. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with GI mucosa leading to higher bioavailability and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance [4-6].

FDDS are preferred as they are economic and has improved patient compliance and they are advantageous for drugs absorbed from the stomach eg: ferrous salts and for drugs meant for local action in the stomach eg:antacids, drugs with narrow absorption window in the small intestine region eg: L-Dopa. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected. Under such circumstances also it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response [9, 10].

The present work is an attempt to develop FDDS in the form of tablets taking Atorvastatin calcium as the model drug. Atorvastatin calcium is a HMG-CoA reductase inhibitor used in the treatment of hyperlipidaemia. Oral bioavailability of atorvastatin calcium is less than 12%. It also undergoes high first pass metabolism. It is absorbed more in the upper part of the GIT.10 So oral absorption of atorvastatin can be increased by increasing gastric retention time of the drug. Thus it is decided to prolong the gastric residence time in terms of making floating gastro retentive drug delivery system to increase drug absorption and hence bioavailability.

In this regard, Atorvastatin calcium gastroretentive floating tablets were prepared by using effervescent and Non Effervescent floating technique using polymers such as Ethyl cellulose, Karaya gum and HPMC K4 M as polymers and gas generating agents like sodium bicarbonate and citric acid and polypropylene foam powder as a selling agent in non effervescent floating tablets. The tablets prepared by direct compression technique by using different polymer concentrations to enhance gastric retention and to increase its bioavailability and duration of action.

MATERIALS AND METHODS

Materials

Atorvastatin calcium was procured from Aristo pharmaceuticals Ltd., Ethyl cellulose, Karaya gum and HPMC K4 M were purchased from S.D. Fine Chemicals (Mumbai, INDIA), sodium bicarbonate and other excipients were procured from spectrum pharma research solutions, Hyderabad.

Preparationof floating tablets Bydirect compressionmethod[12]

All ingredients were collected and weighed accurately. Drug with polymers were sifted and passed through sieve #60 and then the remaining excipients were rinsed over after pre blending all ingredients in mortar for 15minutes. The entire mixture was blended for 5minutes. Then magnesium stearate was added and blended again for 5-6 minutes, lubricated powder was compressed under 8mm punch of tablet punching machine, (Cadmach model DC16 16-Station Tablet Press). The composition of different formulations is shown in the above tables.

EVALUATION OF FORMULATIONS

Pre compressaion parameters

It includesAngle of repose, Bulk density, Tapped density, Cars index,Hausners ratio.

Pre compressaion parameters

It includesWeight variation, Hardness, Friability, Thickness and diameter, Drug content, *In-vitro* buoyancy studies, Swelling index and *In-vitro* dissolution studies.

RESULTS AND DISCUSSION

Gastro retentive floating tablets were formulated by Atorvastatin calcium by Effervescent technique (i.e., from F1-F9) and by Non effervescent technique (i.e.,F10-F18).The formulated tablets have shown the results as given below:

UV Spectra of Atorvastatin calcium at 10µg/ml concentration. Wavelength of maximum absorption in 0.1N HCL solution was found to be 243nm, with uvrange of Atorvastatin calcium was found to be 2-12mcg/ml with a regression value of 0.999.

Compatability studies by FT-IR

From the compatability studies it was concluded that the functional groups that were presented in the pure drug were present in the optimized formulation with very minute changes, from this we can concluded that the drug and excipients have no interactions.

In vitro floating buoyancy studies

All the formulated tablets were evaluated for the buoyancy studies for the determination of Floating Lag Time and Total Floating Time. The formulations having higher polymer concentrations exhibits total floating time for more than 12hours than the other formulations.

Swelling Studies

From the swelling studies of the folating tablets it was identified that the tablets formulated by effervescent technique have higher swelling index than the Non effervescent floating tablets, among them karaya gum having 90mg have higher swelling index.

IN-VITRO DRUG RELEASE STUDIES

In-vitro drug release data of Atorvastatin calcium floating tablets by effervescent technique

From the drug release studies of the gastro retentive floating tablets of Atorvastatin calcium formulated by effervescent technique the maximum amount of drug release was found in F6 formulation containing karaya gum(90mg) as a rate retarding polymer as it has higher efficiency for retarding the drug release in the dissolution medium.

So the drug release kinetics were studied for the F6 formulation, and it follows zero order drug release and the drug release mechanism was found to be super caseII transport mechanism.

In-vitro drug release data of Atorvastatin calcium floating tablets by Non-Effervescent technique

The in vitro drug release profiles of the formulations F1-F9 shows maximum drug release in F6 formulation containing karaya gum in higher concentration i.e.,90mg.

Whereas the formulations F10-F18 formulated by using Non Effervescent floating technique the maximum drug release was found in the F12 formulation containing carbapol 940(90mg).

While comparing the effervescent and Non effervescent floating techniques the maximum drug release was found in the F6 formulation when compared with F12 formulation.

The drug release kinetics of the optimized formulation (F6) of the Atorvastatin follows zero order drug release with super case transport mechanism.

COMPOSITION OFATORVASTATIN CALCIUM FLOATINGTABLETS

Table5.8: Composition of Atorvastatin calcium floatingtablets by Effervescent technique

Ingredients(mg)	F19	F20	F21	F22	F23	F24	F25	F26	F27
Atorvastatin calcium	40	40	40	40	40	40	40	40	40
Carbapol 940	30	60	90	-	-	-	-	--	-
Karaya gum	-	-	-	30	60	90	-	-	-
HPMC K 100M	-	-	-	-	-	-	30	60	90
PVP K30	20	20	20	20	20	20	20	20	20
MCC	98	68	38	98	68	38	98	68	38
NAHCO3	50	50	50	50	50	50	50	50	50
Citric acid	5	5	5	5	5	5	5	5	5
Mg -stearate	3	3	3	3	3	3	3	3	3
Talc	4	4	4	4	4	4	4	4	4
Total wt (mg)	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Table5.9: Composition of Atorvastatin calcium floatingtablets by Non-Effervescent technique

Ingredients(mg)	F28	F29	F30	F31	F32	F33	F34	F35	F36
Atorvastatin calcium	40	40	40	40	40	40	40	40	40
Carbapol 940	30	60	90	-	-	-	-	--	-
Karaya gum	-	-	-	30	60	90	-	-	-
HPMC K 100M	-	-	-	-	-	-	30	60	90
PVP K30	6	6	6	6	6	6	6	6	6
Polypropylene foam powder	50	50	50	50	50	50	50	50	50
MCC	117	87	57	117	87	57	117	87	57
Mg -stearate	3	3	3	3	3	3	3	3	3
Talc	4	4	4	4	4	4	4	4	4
Total wt (mg)	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Table:Precompression parameters & Post compression parameters:

Parameters	Range	Parameters	Range
Angleof repose (θ)±SD	22.06±0.36-29.36±0.84	**Average wt in (mg)±SD**	248.4±0.824 - 250.12± 0.748
Bulk density (gm/cm)±SD	0.252±0.36 -0.288±0.41	**Hardness (Kg/cm2)±SD**	4.269±0.175 - 5.120± 0.166
Tappeddensity (gm/cm) ±SD	0.288±0.01-0.329±0.24	**Diameter in (mm)±SD**	7.86± 0.058-8.27± 0.174
Hausnerratio (HR)±SD	1.10±0.18-1.19±0.28	**Thickness in (mm)±SD**	3.012± 0.126-3.679± 0.246
Carrindex (C.I)±SD	8.681±0.73-16.28±0.22	**Friability (%)±SD**	0.139± 0.018-0.712± 0.005
		Drug content (%)±SD	88.468±0.45-99.341±0.514

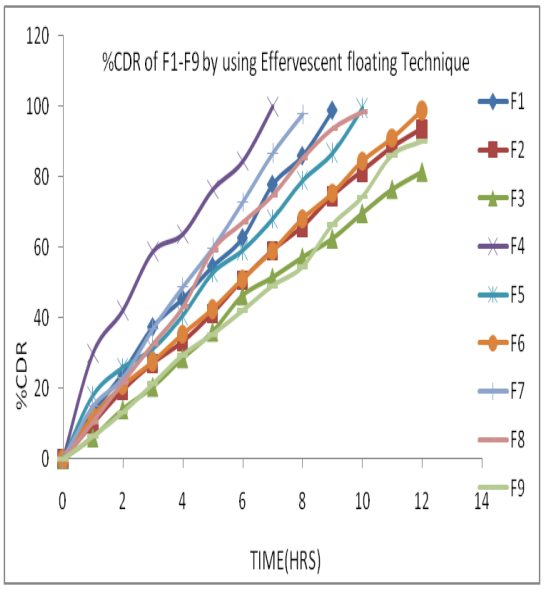

Fig:%CDR of F1-F9

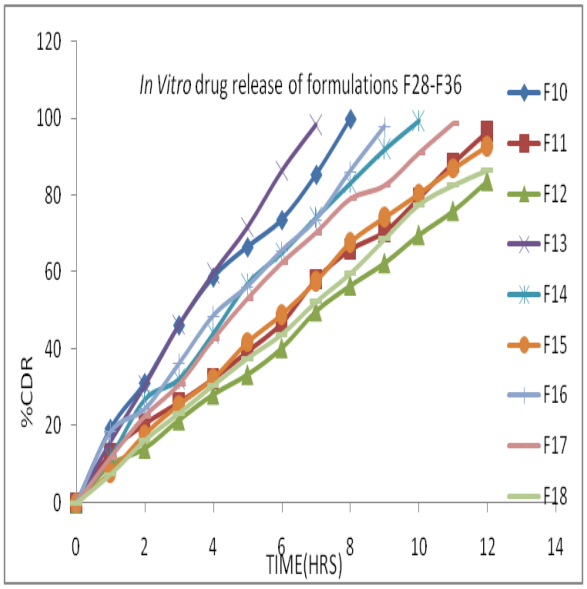

Fig: %CDR of F10-F18

CONCLUSION

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so 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 the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

So for increasing the gastric retention time of the some poorly acidic absorption drugs were selected for increasing the gastric retention time for increasing the bioavailability of the drug.

From the results obtained it was concluded that the in vitro drug release profiles of the formulations F1-F18 the maximum drug release was found in the F6 formulation containing karaya gum(90mg) as a rate retarding polymer formulated by using Effervescent floating technique.

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