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FORMULATION, DEVELOPMENT AND EVALUATION OF GASTRO –RETENTIVE DRUG DELIVERY OF ATORVASTATIN CALCIUM

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ABSTRACT:
The aim of the present work isto develope a gastro retentive floating dosage form of Atorvastatin calcium because of its narrow absorption window in the upper gastrointestinal tract. It has a oral bioavailability of less than 12%. It also undergoes high first pass metabolism. Gastroretentive floating tablets of atorvastatin calcium were formulated by using polymer (HPMC K100M and Carbopol 974P) and gas generating agent (sodium bicarbonate and citric acid) in order to enhance the bioavailability .The formulations were evaluated for physiochemical parameters such as hardness, friability, weight variation, swelling studies, in vitro-buoyancy studies and invitrorelease studies. All the tablets have shown floating duration for more than 12hrs. It was found that formulation containing Carbapol 974P and HPMCK100 in combination of 1:1 shows better floating behavior with good release profile.All the formulations followed zero order kinetics and Non-fickian diffusion mechanism. Fourier transform infrared (FTIR) and Differential scanning colorimetry (DSC) studies revealed no interaction between the drug and polymers.
Key Words: Gastroretentive, Atorvastatin calcium, bioavailability, physiochemical parameters.

INTRODUCTION:

The design of oral-controlled drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as inability to restrain and localize the drug delivery system (DDS) within desired regions of the GI tract and the highly variable nature of gastric emptying process. It can be anticipated that depending upon the physiological state of the subject and the design of pharmaceutical formulations the emptying process lasts from few minutes to 12 hrs. This variability in turns may lead to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine. The gastric emptying time (GET) in humans is normally averages 2-3 hrs, through the major absorption zone (stomach or upper part of the intestine) can result in incomplete drug release from DDS leading to diminished efficacy of the administered dose. Thus, control of placement of DDS in specific region of the GI tract or drugs with stability problem. The intimate contact of theDDS with the absorbing membrane has the potential to maximize the drug absorption and may also influence the rate of drug absorption. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities .[(1)]

Drugs that are required to be formulated into GRDDS include:
1) Drugs that are primarily absorbed in the stomach.
2) Drugs acting locally in the stomach.
3) Drugs with a narrow window of absorption.
4) Drugs those are poorly soluble at alkaline pH.
5) Drugs that degrade in the colon.

Mechanism of Floating Systems:

FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the GERfor a prolonged period of time. While the system is floating on the gastric contents (given in the Figure), 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. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.[(2)]

MATERIALS:

Atorvastatin was received as a gift sample from Maan Pharmaceuticals ltd, Mehsana. Carbapol 974P and HPMC K100 were received by Otto chemiepvt ltd, Mumbai, All other reagents and chemicals used were of analytical grade.

Formulation table 1: Atorvastatin calcium tablet:

Ingredients (mg)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Atorvastatin calcium	40	40	40	40	40	40	40	40	40
HPMC K100	10	20	30	-	-	-	15	5	25
Carbapol974P	-	-	-	10	20	30	15	25	5
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20
Citric acid	10	10	10	10	10	10	10	10	10
Dicalcium Phosphate	38	28	18	38	28	18	38	28	18
Total	120	120	120	120	120	120	120	120	120

FORMULATION OF FLOATING TABLET [3, 4, 5, 6]

Floating tablet containing Atorvastatin calcium was prepared by direct compression technique using varying concentration of different polymers. All the powders were weighed accurately. Then all other ingredients were blended uniformly in glass mortar. The blend was compressed in to tablets having average weight of 120 mg using a rotary single punch tablet machine (Karnavati, Ahmadabad).

CHARACTERISATION OF TABLET:

1. Hardness[8]

Hardness is defined as force is required to crushing the tablet in.The hardness was measured with Monsanto hardness tester or the Pfizer tester.The tablets were placed diametrically between two and togetheplunger and the lower plunger is kept in contact with tablet to read as zero.

2.Thickness and Diameter[8]

The thickness and diameter of minitablets were determined with the help of Vaniercaliper.The average diameter and thickness of the tablet was calculated. The test passed if none of the individual diameter and thickness value deviated by ± 5% of the average.

3. Friability[8,17]

The tablets were subjected to the test of friability with initial weight (Wi) almost equivalent to 6.5 gm of the tablets. The tablets were allowed to fall on itfrom height of 6 inches while the friabilator drum was (Wf) of the tablet after subjecting to friability was noted and the friability was calculated according to formula.

Friability = $\frac{Wf- Wi}{Wf}$

Where, Wi- initial weight of tablet

Wf-Final weight of tablet

The friability of tablets should be within 0.5% to 1% are considered acceptable.

4. Weight variation test[8]

Randomly selected 20 tablets were weighed accurately and together in a single pan balance. The average weight was noted and standard deviation was calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differ by more than double percentage limit.

5. Content uniformity [8]

5 tablets were taken and powdered. From that sample equivalent to 25mg of drug was taken and transferred to 100ml volumetric flask. Methanol(20ml) was added and gently heated on water bath to dissolve the drug , cooled to room temperature and volume was made up to mark with methanol. This was filtered. From that filtrate 1ml was taken and diluted 0. 1 HCL and absorbance of this solution was measured as per analytical method.

COMPATIBILITY STUDY:

Compatibility study of pure drug Atorvastatin calcium with excipients was carried out prior to the preparation of floating tablets.I.R. spectra of pure drug and combination with polymer were obtained.The obtained spectra were interpreted with standard spectra for identification of pure drug. Atorvastatin calcium - HPMC K100 and Atorvastatin calcium - Carbapol974P (1:1)were studied for Compatibility study using FTIR technique.Position of peaks was compared with IR spectra of Atorvastatin calcium**.**

INVITRO BUOYANCYSTUDY[7, 8]

The in vitro buoyancy was performed for the all six formulations as per the method described by Rosa et al. The randomly selected tablets from each formulation were placed in a250 ml beaker, containing 200ml of 0.1 N HCL. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the period up to which the tablet were remained buoyant is determined as Total Floating Time.

SWELLING STUDY[7,8]

The swelling index of the polymer can be measured by their ability to absorb water and swell. Three tablets from each formulation were kept in a petridish containing 0.1 NHCL. After a selected time interval the tablets were withdrawn blotted to remove excess of liquid and again weighed the tablet. Swelling index of the tablets was calculated by following formula.

INVITRO DISSOLUTION STUDY([9,10,11]

The In vitro dissolution study was performed by using a USP Dissolution testing Apparatus at a rotational speed of 50 rpm.The dissolution test was performed using 900ml of 0.1 N HCL (pH 1.2) was used as the dissolution medium. The tablet was placed in the vessel and the temperature was maintained at 37 ±0.5. A sample of with(5 ml) of the solution was withdrawn from the dissolution apparatus at a specified time interval for 12 hours and the same volume were replaced with fresh dissolution medium. The withdrawn sample s were filtered through 0.45 um whatman filter paper an diluted with a required volume of plain dissolution medium kept at 37 .The collected samples were analyzed at λ max 246nm using a Lab India 3000 UV-visible double beam spectrophotometer against 0.1 N HCL as blank.

CURVE FITTING ANALYSIS- DRUG RELEASE KINETICS [12-16)]

The release data obtained from various batches were studied with respect to effect of drug: polymer ratio, diluents ratio. To analyze the mechanism of drug release from the formulation, the dissolution profile of all the batches were fitted to zero order, first-order, Higuchi, Korsemeyer and Peppas, to ascertain the kinetic modelling of drug release.

EVALUATION OF FLOATING TABLET:

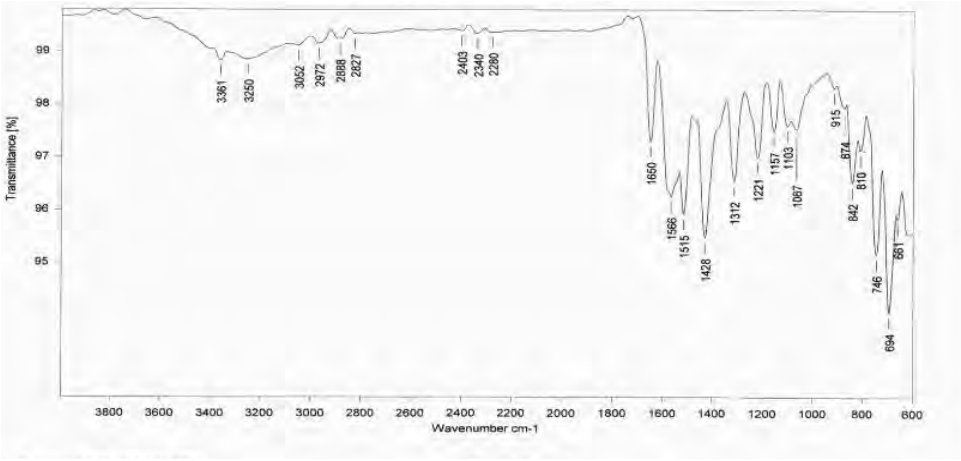

Fig.1:FTIR spectra of Atorvastatin calcium drug

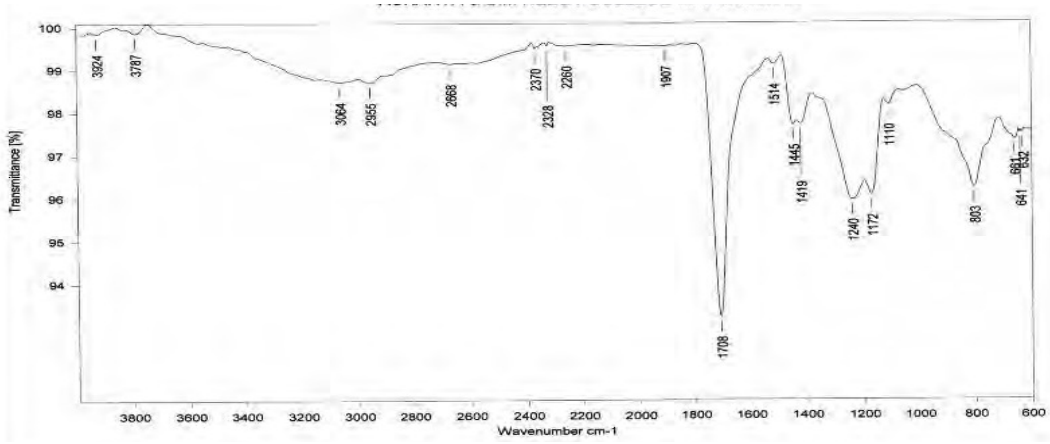

Fig.2: FTIR spectrum of Atorvastatin +Carbapol974P(Formulation F4)

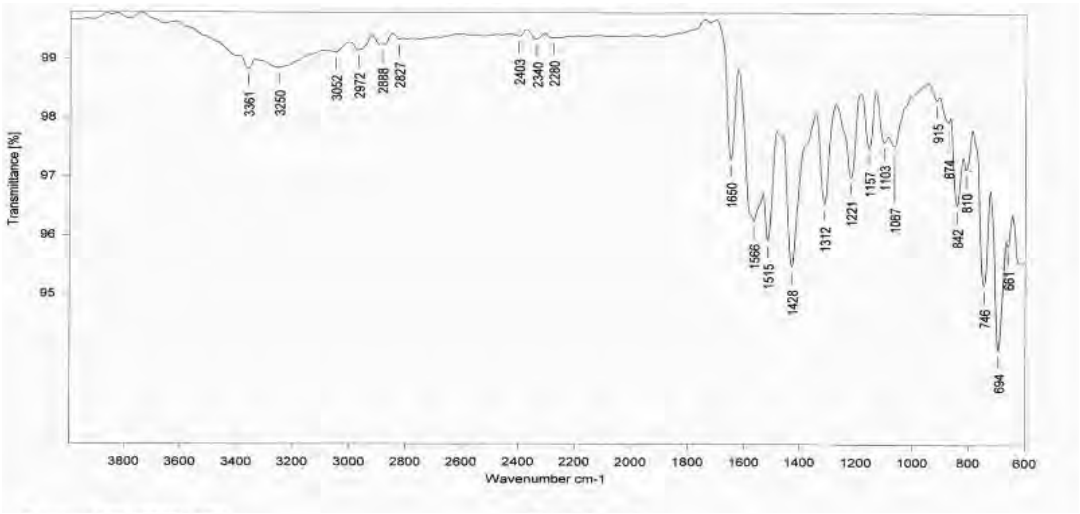

Fig.3:FTIR spectrum of Atorvastatin calcium+HPMCK100M(Formulation F1)

All characteristic peaks of Atotvastatin calcium were present in spectra thus indicating compatibility between drug and excipients.

Table1:Post compression parameters of designed formulations

Formulation code	Weight variation *(mg)	Thickness *(mm)	Hardness *(kg/cm^2)	Friability (%)	Content Uniformity (%)
F_1	100.35±3.39	2.15±0.13	4.5±0.5	0.18	99.41
F_2	102.3±3.92	2.35±0.19	4.6±0.28	0.20	98.82
F_3	99.5±3.85	2.28±0.14	4.3±0.28	0.60	98.22
F_4	104.5±3.94	2.0±0.17	3.5±0.5	0.17	98.49
F_5	99.6 ±4.09	2.12±0.12	4.6±0.28	0.17	98.50
F_6	102.8 ±3.6	2.23±0.25	4.3±0.76	0.20	99.31
F_7	101.45±3.06	2.05±0.19	4.0±0.5	0.17	99.01
F_8	101.2 ± 2.76	2.05±0.12	4.5±0.5	0.17	98.82
F_9	99.95±2.79	2.10±0.2	4.5±0.5	0.17	99.19

In vitro Buoyancy studies:

Table2: Floating Lag Time and TFT of designed formulations

Batch Codes	Floating lag time(sec)	Total Floating Time(Hrs)
F1	10.58	15
F2	10.57	15
F3	10.78	20
F4	10.59	17
F5	10.65	16
F6	10.66	18
F7	10.33	24
F8	10.45	19
F9	10.52	20

Swelling study:

Table 3:The percentage swelling of the tablets at various time intervals

	SwellingIndex (%)								
Time (Min)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
30	36.69	39.00	45.84	39.71	39.25	41.72	41.31	40.08	39.71
60	50.36	44.96	48.99	46.85	46.70	49.64	48.92	47.70	46.80
120	57.12	54.46	56.73	55.28	54.29	57.98	57.12	56.17	52.90
180	63.30	60.00	63.61	60.00	60.17	62.30	62.87	60.92	58.58
240	70.93	66.66	70.77	68.28	69.05	69.78	69.49	67.81	66.52
300	76.69	72.76	74.78	73.57	73.06	75.82	74.38	73.70	72.76
360	89.20	83.68	86.53	86.42	85.96	88.77	88.05	86.06	85.81

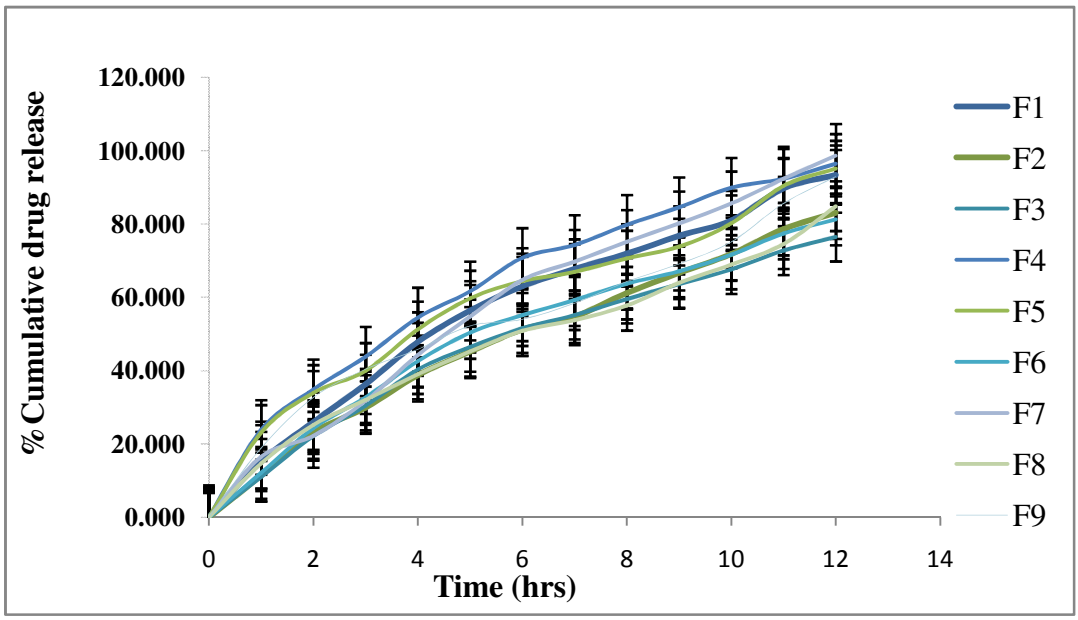

Fig. 4 :In-vitro drug release:

The formulations F1, F2 and F3 contain HPMC K100 at varying concentrations. The higher initial drug concentrations from F1 to F3 showed the release 93.35±5.31, 83.07±4.0, 76.41±0.48 respectively. So as the concentration of HPMC k100 is increased the initial drug concentration in the dissolution medium decreases as well as showed sustained release. So varying concentration of HPMC K100M affects the drug release.

The formulation F4, F5 and F6 contain various concentration of Carbapol 974P. Formulations F4,F5 and F6 showed the release 96.37±0.76, 95.10±1.16 and 81.9±1.17 respectively. It was observed that as the concentration of polymer increased, it shows decrease in drug release.

The formulations F7,F8 and F9 contain combinations of both polymer HPMC K100 and Carbapol 974P. These show the drug release 98.55±5.7, 84.84±2.83 and 92.95±6.65 respectively at the end of 12 hrs. So the tablet containing optimized concentration of both polymers showed better control drug release of 98.55±5.7 up to 12 hrs. In all the formulations polymer concentration greatly affected the release of the drug. The drug release rate was inversely proportional to the polymer concentration present in the matrix

DRUG RELEASE KINETIC OF ATORVASTATIN TABLET:

Table 4: Drug release kinetic of Atorvastatin calcium tablet

Formulation code	R^2				N
	Zero order	First order	Matrix	Korsmeyer Peppas	Korsmeyer Peppas
F_1	0.9540	0.9679	0.9836	0.9756	0.7234
F_2	0.9971	0.9915	0.9738	0.9982	0.7754
F_3	0.9918	0.9976	0.9839	0.9915	0.7494
F_4	0.9931	0.9750	0.9966	0.9982	0.5748
F_5	0.9095	0.9401	0.9932	0.9957	0.5580
F_6	0.9473	0.9963	0.9854	0.9914	0.7336
F_7	0.9951	0.9813	0.9707	0.9931	0.7671
F_8	0.9908	0.9688	0.9811	0.9976	0.6666
F_9	0.9326	0.9297	0.9852	0.9915	0.5848

The Zero order Model plot of optimized formulation (F-7) was found to be highly linear, and close to infinity as indicated by their high regression (R^2) value as 0.998. Therefore it was ascertained that the drug permeation from these formulations could follow Zero order kinetic.

The Peppas model shows the drug release mechanism deviates from Fick's laws and shows anomalous transport. This is demonstrated by following equation:

$$M_t / M_\infty = k.t^n$$

Where M_t is the drug released at time t, M_∞ is the quantity of drug released at infinite time, k is the kinetic constant and *n* is the release exponent.

In case of controlled or sustained release formulations diffusion, swelling and erosion are the three most important mechanisms.. The release exponent '***n***' is indicative of the mechanisms of the formulation. A value of 0.5 is indicative of diffusion-controlled drug release and fickian diffusion and 1.0 indicates swelling-controlled drug release. A value of **'*n*'**between 0.5-1.0 indicates anomalous transport. *i.e.* both swelling and diffusion mechanisms and n be efficient in describing non-fickian diffusion.

To confirm diffusion mechanism, data were fitted to Korsemeyer-Peppas model. The F7 formulation showed R^2coefficient=0.99, with slope (n) values 0.760. A value of n=0.760 indicates non fickian or anamolous release. In the non-fickian case, the rate of drug release is due to the combined effect of drug diffusion and polymer relaxation.

SUMMARY:

The aim of this research work was to design and evaluate floating tablets of Atorvastatin calcium, in view to improve patient compliance and therapeutic action. The floating tablets of Atorvastatin calcium were prepared by direct compression method by using polymers HPMC K100 and Carbapol 974P and Sodium Bicarbonate as an effervescent agent. Concentrations of both polymers in tablets were optimized by preliminary studies. It was revealed that the concentrations of both polymers had significant effect on floating lag time and drug release characteristics from dosage form. The tablets were evaluated for friability, drug content and *in-vitro*floating lag time and drug release studies.

The drug Atorvastatin calcium can be formulated in a floating tablets using optimum amount of Sodium bicarbonate and HPMC K100 and Carbapol 974P.

CONCLUSION:

This study evaluated the suitability and feasibility of Floating tablets of Atorvastatin calcium with a view of enhancing patient compliance and bioavailability. Based upon the experimental findings it was concluded that:

1) Gastro retentive Floating tablets of Atorvastatin calcium using Carbapol 974P and HPMC K100 were successfully prepared by direct compression technique and polymers were compatible with each other as indicated by FT-IR study.
2) In the optimization studies of Drug-polymer, it was observed that increase in polymer concentration shows better sustained release effect. It was found that formulation containing Carbapol 974P and HPMCK100 in combination of 1:1 shows better floating behavior with good release profile. Even it shows better tablet characteristics. Thus, formulation containing 1:1 concentration of carbapol 974P and HPMCK100 was selected for the further study.
3) Formulation F7 was found best formulation among developed formulation it contains Carbapol 974P and HPMCK100 in the ratio 1:1. It shows higher % of release in 0.1 N HCL (R^2 0.986) with better effect, good floating behaviorand all other parameters(Hardness, Friability etc).
4) All the formulations in this study were best expressed by Zero order kinetic release profile. To confirm the diffusion mechanism, the data were fitted to Korsmeyer-Peppas model. The n values for formulations F1 to F9 ranged from 0.57 to 0.77, indicating that the release mechanism was non-Fickian or anomalous release.

Thus, the formulated *Gastroretentive floating tablet of Atorvastatin calcium* seems to be a promising formulation of Atorvastatin with good buoyancy study and better release profile.

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