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DESIGN DEVELOPMENT AND EVALUATION OF GASTRO RETENTIVE FLOATING MICROSPHERES OF ATAZANAVIR SULFATE

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ABSTRACT: The purpose of present study was to formulate the gastro-retentive floating microspheres of atazanavir sulfate to be retentive in the stomach for prolonged period of time. The gastro-retentive floating microspheres were prepared by double emulsion $w_1/o/w_2$ solvent evaporation technique and characterization for particle size, SEM, floating time, FTIR, DSC, and entrapment efficiency. The *in-vitro* drug release studies and *in-vitro* drug kinetics were performed for different formulations. FTIR and DSC studies revealed that the drug is compatible with excipients. The floating time of the floating microspheres was found to be > 12h. The particle size of all the formulations was evaluated by optical microscopy method. Formulation F1 - F4 comprising HPMC as rate retarding polymer exhibits an average particle size of about 515.25 μ m and microspheres F5 – F8 prepared with eudragit exhibit a mean particle of about 611.4 μ m. Eudragit formulations exhibit an increased entrapment efficiency which is due to its large particle size and increased viscosity. All batches prepared show an initial burst release followed by sustained release. Formulation F 1 to F4 exhibits an *in vitro* release of 67.8%, 70.9%, 77.8% and 87% respectively at the end of 10th h. Formulation F5 to F8 exhibits a release of 36.1%, 54.6%, 57.6% and 67.8% respectively at the end of 10th h. Among all the formulations, F4 prepared with combination of HPMC and ethyl cellulose exhibits sustained release behavior. The developed floating microspheres assure the delivery of drug for a prolonged period of time.

INTRODUCTION: Gastro retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over the gastric contents the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

Prolonged retention in the upper GIT tract can greatly improve the oral bioavailability and their therapeutic outcome. The pH dependent solubility and stability level plays an important role in its absorption. Microencapsulation has been used as a one of the methods to deliver drug in control and sustained manner therefore it is evident that a gastric floating based drug delivery system will be best suit the purpose of our dosage form design¹.

Various approaches have been pursued to increase the retention of the dosage form in the gastrointestinal tract. These techniques make use of the various physiological and anatomical characteristics of the stomach. Expandable systems, bio-muco adhesive system, floating drug delivery

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systems and combination of floating, mucoadhesive and swelling systems^{2,3}. Floating microspheres on contact with the gastric fluid forms a colloidal barrier and consequent drug release⁴. The swollen polymer lowers the density and confers buoyancy to the microspheres. The floating drug delivery system was broadly classified as effervescent (gas generating) and non effervescent systems. The effervescent systems upon arrival in the stomach; release carbon dioxide and cause the formulation to float in the stomach. These devices contain a hallow deformable unit that converts from a collapsed to an expanded position and returns to the collapsed position after a predetermined amount of time to permit the spontaneous ejection of the inflatable system from the stomach.

Non effervescent systems after swelling forms unrestrained imbibition of gastric fluid that prevents their exit from the stomach. The swollen polymer lowers the density. The air trapped by the swollen polymer confers buoyancy to these dosage forms as a result the drug dissolves in and diffuses out with the diffusing solvent creating a receding boundary within the gel structure⁵. These systems are further classified into hydrodynamically balanced system⁶, microporus compartment system, alginate beads, hallow microspheres/microballons.

Atazanavir sulphate is an anti retro viral drug⁷. It is an azapeptide HIV- protease (PI) which is active against human immuno deficiency virus type I⁸. The solubility of atazanavir sulphate was influenced by the gastric pH⁹.

The hallow microspheres are strict sense, spherical empty particles without core. The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of the drug⁴.

The hallow microspheres were developed by double emulsion solvent evaporation diffusion technique using ethyl cellulose, hydroxyl propyl methyl cellulose, and eudragit E 100 as polymers which provide better encapsulation efficiency^{10, 11, 12}. Ethyl cellulose was used as a retarding polymer

where as HPMC and eudragit E 100 dissolves at gastric pH¹³. The semi synthetic combination of polymers exhibits a sustained effect. The present study is aimed to prepare a gastro retentive floating hallow microspheres drug delivery system of Anti retroviral drug of atazanavir sulfate to increase gastric retention and sustained release formulation of the drug for enhancement of oral bioavailability.

MATERIALS AND METHODS: Atazanavir sulfate was obtained from Therdose Pharma Pvt., Ltd., as gifted sample from Hyderabad. Hydroxy propyl methyl cellulose was obtained from CDH, New Delhi, eudragit E 100 was obtained from CDH, and New Delhi and Ethyl cellulose was obtained from lobachem. Pvt., Ltd., acetone and tween 80 were purchased from SD fine chemicals Ltd., Mumbai. All other chemicals utilized in the research are of analytical grade were purchased from spectra chemical Pvt., Ltd., and Merck, Mumbai.

METHODS:

Preparation of Floating Microspheres of Atazanavir Sulfate: The floating microspheres were prepared by using double emulsion method, based on w/o/w emulsion solvent evaporation technique¹⁴. Microspheres were prepared by using rate retarding polymers such as ethyl cellulose, hydroxyl propyl methyl cellulose and eudragit E 100. Blend of polymers were used in the process. Different batches of atazanavir sulfate microspheres were prepared by varying the concentration of polymers in the formulation. The composition of batches were given in **Table 1**. The internal aqueous phase (W_1) was 0.1 N HCl. The organic phase comprised of mixture of DCM and ethanol (1:1 ratio) and the external aqueous phase (W_2) was distilled water containing 0.5% tween 80. The required quantities of the polymer and drug were dissolved in the mixture of dichloromethane: ethanol and homogenize the mixture to form the primary (W/O) emulsion. The primary emulsion was then injected into W_2 phase comprising 0.5% tween 80 to form the secondary ($W_1/O/W_2$) emulsion. The resultant emulsion was stirred with a propeller type agitator for 2 h to allow the solvent to evaporate. The microspheres formed were filtered, was washed with water and dried overnight at room temperature¹¹.

TABLE 1: COMPOSITION OF ATAZANAVIR SULFATE LOADED POROUS FLOATING MICROSPHERES

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Atazanavir Sulfate	200	200	200	200	200	200	200	200
HPMC Ethyl cellulose	100	200	300	400	—	—	—	—
Eudragit L100	700	600	500	400	700	600	500	400
DCM	—	—	—	—	100	200	300	400
Ethanol	5	5	5	5	5	5	5	5
Tween 80	5	5	5	5	5	5	5	5
Propylene glycol	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	10	20	30	40	10	20	30	40

Determination of Particle Size by Optical Microscopy: The formulated floating microspheres were characterized by optical microscopy for particle size and size distribution. The eye piece micrometer was calibrated with the help of a stage micrometer. The microspheres were dispersed on a glass slide, the size of 300 particles was measured using a micrometer attached with a microscope and the average particle size was evaluated¹⁵.

Morphology Study Using SEM: The morphological characteristics of the samples were studied using scanning electron microscopy (SEM, JOEL-JFC 5300) (S-4800, Hitachi Co. Ltd. Japan). Microspheres were dispersed in distilled water, dripped in aluminum foil and evaporated. The dried microspheres were mounted on a copper stub, coated with gold palladium under vacuum using an ion sputter coater (JEOL JFC 1100E) and then observed under scanning electron microscope¹⁶.

Fourier Transform Infra Red Spectroscopy (FTIR) Analysis: The infrared absorption spectra of pure drug, polymer and floating microsphere formulations were obtained using a FT-IR spectrophotometer (Shimadzu, FTIR- 1800 S). Few mg of samples were pressed into a pellet by mixing with 100 times with KBr at a pressure of about 10 t/in and scanned for IR absorption spectra¹⁷.

Differential Scanning Calorimetric (DSC) Analysis: The physiochemical compatibilities of the optimized formulations were tested by differential scanning calorimetric (DSC) analysis. Thermal characterization of pure drug and microsphere formulations were performed with mettler Toledo, USA. About 10mg of the sample is placed in sealed aluminum pan. The equipment was calibrated with indium. The samples were scanned at 20 °C/min from 50 - 40 °C.

Drug Entrapment Efficiency: The amount of drug encapsulated in the formulated microspheres, was estimated by placing a weighed amount of microspheres in 100ml of 0.1N HCl¹⁸. The solution was filtered in the Whatman filter paper. After the suitable dilution the absorbance was measured at 247 nm using UV spectrophotometer. Based on the absorbance, entrapped efficiency of different formulation was calculated.

$$\% \text{ Drug entrapment} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug loaded}} \times 100$$

Floating Time: Floating behaviour of hallow microspheres was studied in a USP dissolution test apparatus (paddle type) by spreading the microspheres (100mg) on a 0.1 N HCl containing 0.02% tween 80 as surfactant to rise to the surface and float was determined as floating lag time. The lag time is determined by the microspheres rise to the surface and float. The medium was agitated with a paddle rotating at 100rpm and maintained at 37 °C for 12 h.

In vitro Release Study: The *in vitro* drug release study for developed floating microspheres using a modified USP dissolution apparatus type I (basket type). The test material was placed in 900 ml of dissolution media at 37 °C using basket rotating at 50 rpm. 0.1N HCl was used as dissolution medium to study the rate and extent of drug release and to evaluate release kinetics for prediction of release in GI tract. An aliquot medium was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added. Withdrawn samples were filtered by Whatman filter paper. The drug absorbance was determined with UV- visible spectrophotometer (Elico, India) after proper dilution of samples.

Drug Release Kinetic Modelling: To characterize the underlying drug release mechanisms and to optimize the design of a therapeutic device mathematical models are widely employed. The analysis of *in-vitro* release profiles of formulations was done by fitting the release data in several drug release models including zero order, first order,

Higuchi and Korsmeyer- Peppas. These models are used to characterize drug dissolution / release profile¹⁹.

RESULTS AND DISCUSSIONS: The floating microspheres of atazanavir sulphate were prepared by using emulsion solvent evaporation double emulsion technique. Microspheres were prepared by using the polymers ethyl cellulose, hydroxyl propyl methyl cellulose and eudragit E100. A combination of two polymers was used to prepare the microspheres. Ethyl cellulose was used as a retarding polymer where as HPMC and eudragit E 100 dissolve at gastric pH. Therefore a combination is used to obtain a sustained effect.

Particle Size Determination of the Microspheres: The particle size of all the formulations was evaluated by optical microscopy method. Formulation F1 - F4 comprising HPMC as rate retarding polymer exhibits an average particle size of about 515.25 μm and microspheres prepared with eudragit exhibit a mean particle of about 611.4 μm . The mean particle size of microspheres formulated

with eudragit exhibit an increased size than the microspheres formulated with HPMC, the size of the particle was influenced with the addition of increasing concentration of eudragit which was influenced by its viscosity²⁰. The size and size distribution of atazanavir sulphate floating microspheres is shown in **Table 2**.

Surface Morphology of Microspheres: The surface morphology of the floating microspheres were studied using SEM (Scanning Electron Microscope). The SEM images showed that the microspheres surface were porous in nature. The surface of microspheres prepared by HPMC is more porous as compared to those of eudragit E 100¹⁶. The microspheres were individually homogeneously distributed without the evidence of collapsed spheres. The results were shown at **Fig. 1 - 2**.

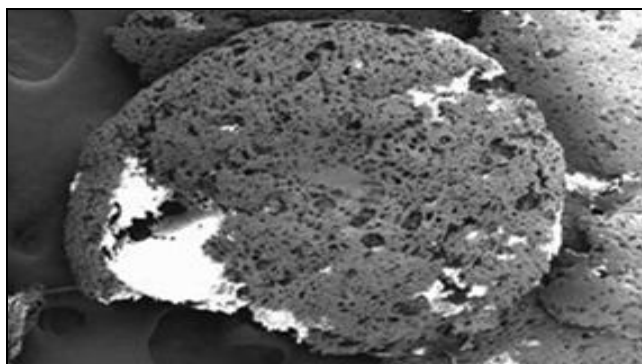
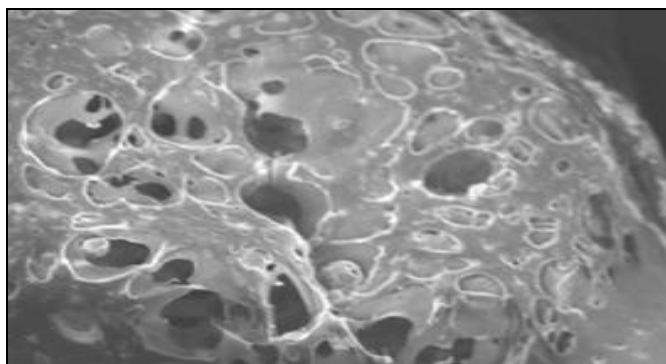


FIG. 1: HOLLOW STRUCTURE OF MICROSPHERES PREPARED WITH HPMC, ETHYL CELLULOSE AND PROPYLENE GLYCOL

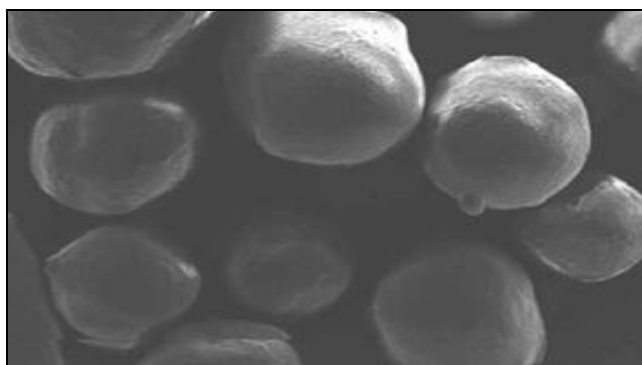
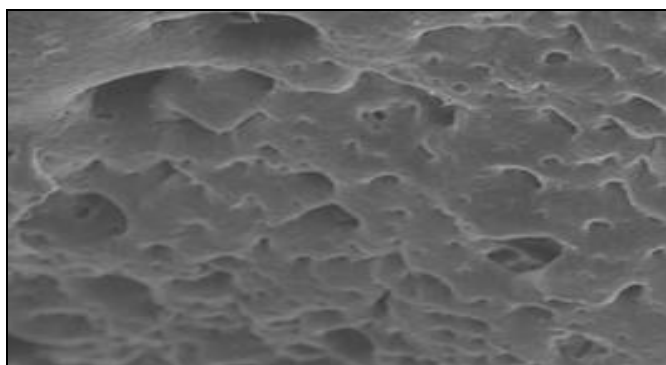


FIG. 2: HOLLOW STRUCTURE OF MICROSPHERES PREPARED WITH EUDRAGIT E 100, ETHYL CELLULOSE AND PROPYLENE GLYCOL

FTIR Spectrum: The IR absorption spectra of a pure drug atazanavir sulfate was taken in the range of 4000 - 600 cm^{-1} using KBr disc and the characteristic peak of the drug were observed¹⁷. The IR spectra of physical mixture and formulation were studied, the results reveals that the

characteristic peak of pure drug was predominantly present, which proves the drug and excipients are compatible. No change in shape of spectra observed, indicating that the drug in presence of excipients remains stable. The results were shown in **Fig. 3 - 7**.

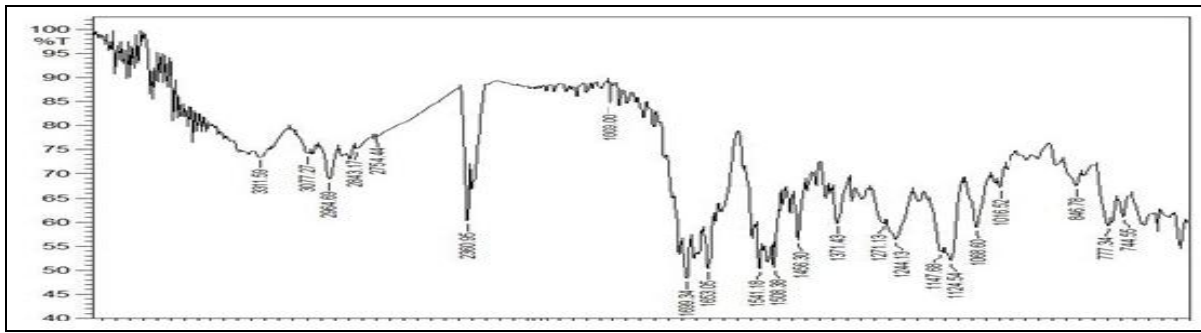


FIG. 3: INFRARED SPECTRUM OF PURE DRUG ATAZANAVIR SULPHATE

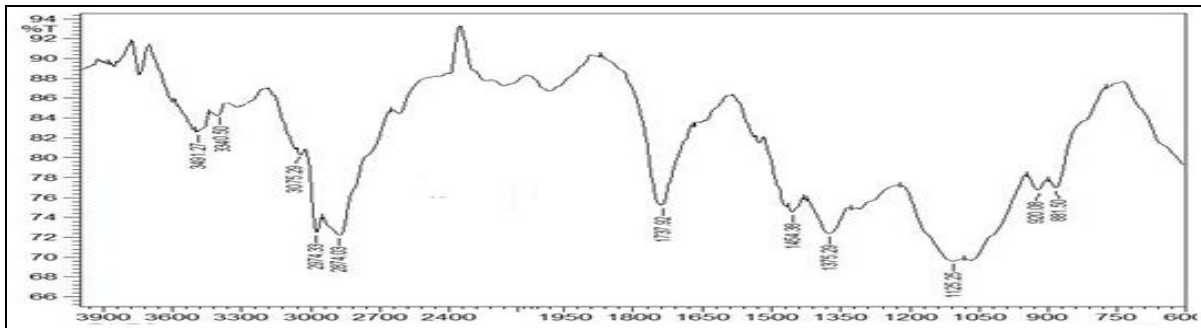


FIG. 4: INFRARED SPECTRUM OF PHYSICAL MIXTURE OF PURE DRUG AND HPMC

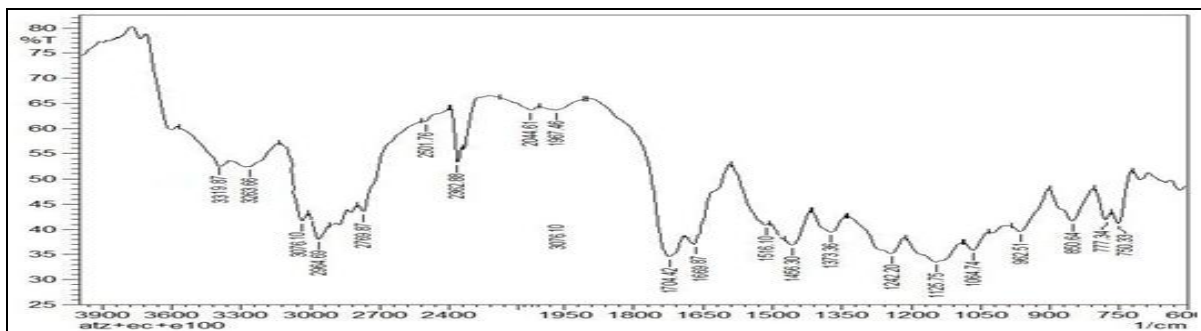


FIG. 5: INFRARED SPECTRUM OF PHYSICAL MIXTURE OF PURE DRUG AND EUDRAGIT E 100

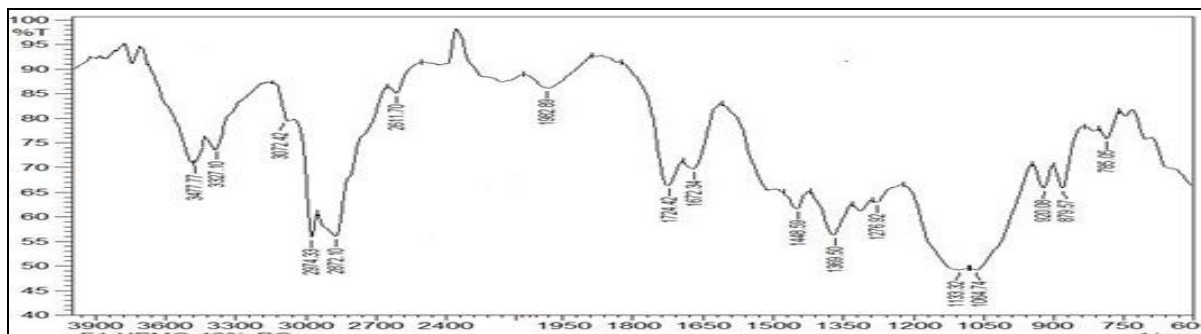


FIG. 6: INFRARED SPECTRUM OF MICROSPHERE FORMULATION WITH HPMC

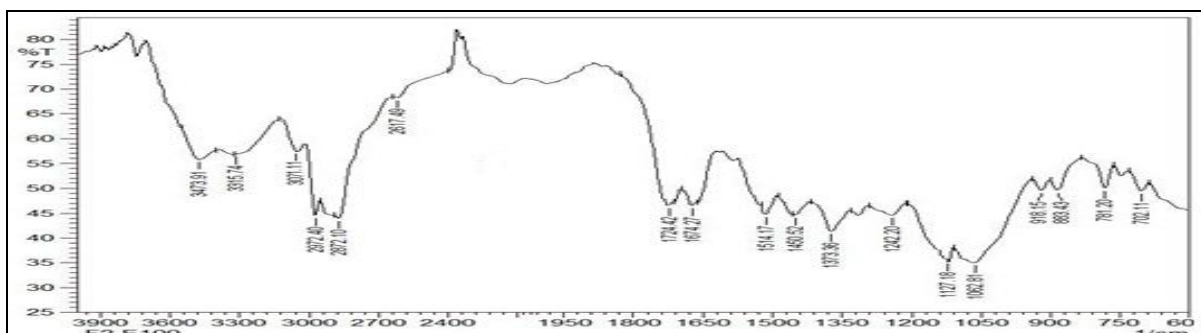


FIG. 7: INFRARED SPECTRUM OF MICROSPHERE FORMULATION WITH EUDRAGIT E 100

Differential Scanning Calorimetric (DSC)

Analysis: The DSC thermograms of atazanavir, physical mixture with EC and HPMC and formulation are shown in **Fig. 8 - 9** the thermogram of pure atazanavir shows a sharp endothermic peak at 197.37 °C which corresponds to the melting point of atazanavir. The thermogram of physical mixture exhibits the endotherm at 196.56 °C having less sharpness which is due to melting. The occurrence of endotherm is more or less same region that indicates no well defined interaction. The reduction in the intensity may be due to less

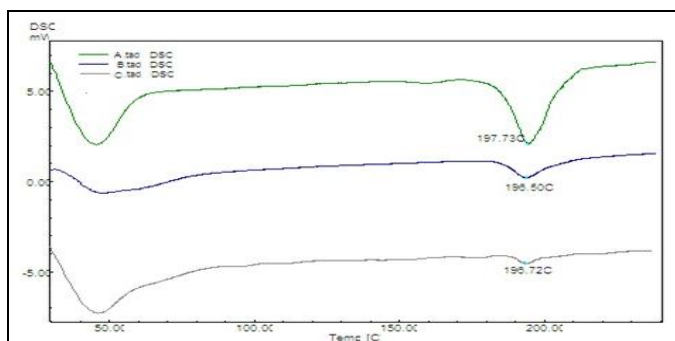


FIG. 8: DSC THERMOGRAM OF A) PURE DRUG B) PURE DRUG AND HPMC, EC PHYSICAL MIXTURE C) PURE DRUG AND HPMC, EC FORMULATION

Drug Entrapment Efficiency: The amount of drug encapsulated in each of polymeric floating microspheres was determined by calculating the amount of drug that could be recovered after dissolving the microspheres in dichloromethane: ethanol mixture as shown in **Table 2**. The efficiency of encapsulation of all formulations were investigated. Eudragit formulations exhibit an increased entrapment efficiency which is due to its large particle size and increased viscosity^{14, 20}. The amount of the internal aqueous phase had an influence on the entrapment efficiency. The entrapment efficiency increased as the amount of the internal aqueous phase decreased. This can be attributed to the increase in the viscosity of the

proportion of drug in the physical mixture. The thermogram of drug loaded floating microsphere exhibits similar shape and position to that of polymer and the peak corresponding to the melting point of free drug was disappeared. Absence of detectable melting peak of drug in the formulation indicates amorphous or molecular dispersed state of entrapped drug. The reduction in peak intensity indicates that microsphere formulation process have a negative effect on the crystallinity of the drug.

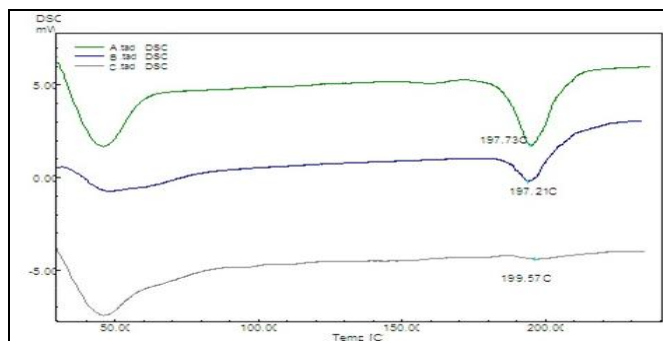


FIG. 9: DSC THERMOGRAM OF A) PURE DRUG B) PURE DRUG AND EUDRAGIT E 100, EC PHYSICAL MIXTURE C) PURE DRUG AND EUDRAGIT E 100, EC FORMULATION

primary emulsion at lower amounts of the W1 phase. Because of the high internal viscosity a lower amount of active agent reached the external aqueous phase leading to increased entrapment efficiency.

Floating Time: The floating lag time of all the formulations were studied. The densities of floating microspheres were found to be less than the density of gastric fluid, therefore tended to float over gastric fluid. The larger the particle size, the longer the floating time, all the formulations exhibit a floating time of not less than 12 h. The result of floating time is shown in **Table 2**.

TABLE 2: PERCENTAGE ENTRAPMENT EFFICIENCY, PARTICLE SIZE AND FLOATING TIME OF FORMULATION BATCHES F1 – F8

Formulation code	Drug/polymer ratio	Entrapment efficiency (%)	Average particle size (µm)	Floating time
F1	1:8	63	519.2	> 12 h
F2	1:8	62	525.4	> 12 h
F3	1:8	65	512.1	> 12 h
F4	1:8	64	504.3	> 12 h
F5	1:8	58	529.4	> 12 h
F6	1:8	60	587.6	> 12 h
F7	1:8	62	643.8	> 12 h
F8	1:8	60	684.8	> 12 h

In-vitro Drug Release Studies: The release rate of atazanavir sulfate from microspheres was determined using USP dissolution testing apparatus I (Basket type). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5 °C and 50 rpm. The formulations F1- F4 were prepared by using HPMC and ethyl cellulose as rate controlling polymer. The release of formulations was attributed by incorporation of propylene glycol as plasticizer. The effect on the drug release profile was studied. The formulations show a biphasic pattern with initial burst release. Formulation F 1 to F4 exhibits a release of 67.8%, 70.9%, 77.8% and 87% respectively at the end of 10th hour. The results were shown in **Fig. 10**.

The formulations F5- F8 were prepared by using eudragit E 100 and ethyl cellulose as rate controlling polymer. The effect on the drug release profile was studied. Formulation F5 to F8 exhibits a release of 36.1%, 54.6%, 57.6% and 67.8% respectively at the end of 10th hour. The results were shown in **Fig. 11**. All the formulations showed a burst release *i.e.* an initial high release rate. This can be attributed to the drug present on

the surface of the microspheres and also to the rapid hydration of the polymer on coming in contact with the dissolution media. The dissolution studies showed an enhanced rate of dissolution of atazanavir sulfate from the microspheres. The rate of release of drug from HPMC formulations were higher than eudragit E 100 formulations, this may be attributed to the acrylic polymer property of eudragit E 100 which gave lower release and hydrophilic nature of HPMC which shows higher release^{19, 20}.

The release of all formulations was attributed by incorporation of propylene glycol as plasticizer. A comparative study revealed that as the amount of plasticizer increased in the formulations the cumulative drug release also increased. This was because propylene glycol increased the hydrophilicity and porosity of the polymer and thus increased the drug release from the porous polymeric matrix. Among all the batches formulated, formulation F4 comprising 40% propylene glycol showed about 25% drug release in the 1st hour and an estimated drug release of about 87% at the end of 10th h.

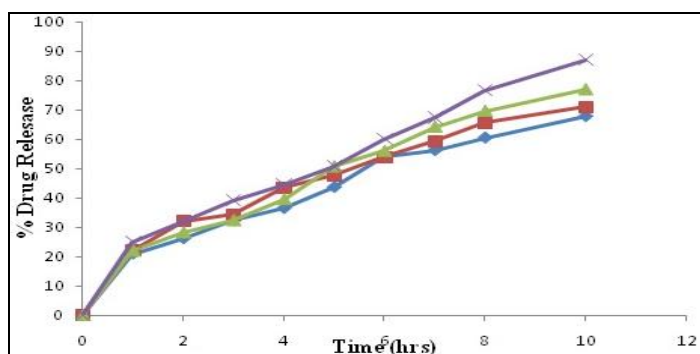


FIG. 10: COMPARATIVE RELEASE PROFILE OF FORMULATIONS F1 TO F4

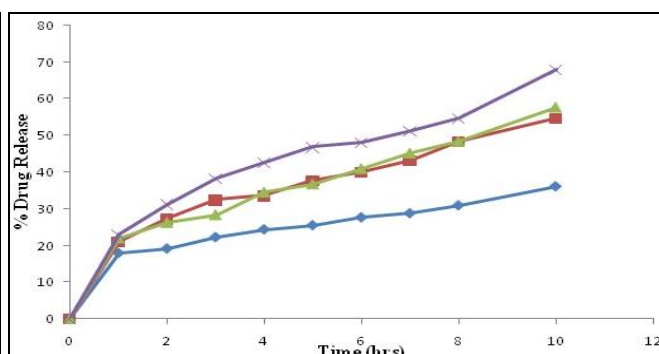


FIG. 11: COMPARATIVE RELEASE PROFILE OF FORMULATIONS F5 TO F8

TABLE 3: KINETIC DATA OF ATAZANAVIR SULFATE LOADED POROUS FLOATING MICROSPHERES

Batch	Zero R ²	First R ²	Higuchi R ²	Peppas R ²
F1	0.9116	0.9761	0.9853	0.5849
F2	0.9116	0.9865	0.9931	0.5962
F3	0.9116	0.9873	0.9744	0.5745
F4	0.9116	0.9495	0.9744	0.5448
F5	0.8017	0.8553	0.9544	0.4918
F6	0.9116	0.9401	0.9855	0.5314
F7	0.9116	0.9583	0.9827	0.5406
F8	0.9116	0.9346	0.9845	0.5413

Drug Release Kinetic Modelling: The release data obtained was fitted to various kinetic models such as zero order, first order, Higuchi, and Peppas

models in order to conclude the mechanism of release of atazanavir sulfate from the developed porous floating microspheres. All the formulations

shows best fit with the highest correlation coefficients for first order followed by Higuchi¹⁹. This indicates that the release of atazanavir sulfate from microspheres is controlled by diffusion. Formulation F4 shows R² value 0.984 which is highest correlation factor with Higuchi. The results were shown in the **Table 3**.

CONCLUSION: The porous floating microspheres of atazanavir sulfate were successfully prepared by w/o/w emulsion solvent evaporation technique. The microspheres formed were spherical and porous surface. The average particle size was found to be 515.25 µm with HPMC and 611.4 µm with eudragit E 100. High percentage of encapsulation was observed with eudragit than with HPMC, where the former exhibits high viscosity. The FTIR and DSC studies reveal the compatibility of drug and excipients. All batches formulated exhibit satisfactory floating and lag time. The *in-vitro* release studies showed an initial burst release followed by sustained release. Among all the formulations, F4 prepared with combination of HPMC and ethyl cellulose exhibits sustained release behavior.

Hence, it is concluded that the developed porous floating microspheres could deliver the drug for a prolonged period of time. Characterised for their drug entrapment efficiency, drug loading, particle size analysis, surface morphology, DSC studies, *in-vitro* drug release behavior and *in-vitro* release mechanism. Eight formulations of microspheres were prepared F1-F8. The formulation giving a best release profile. It was observed that all the formulation followed Higuchi model.

All the formulations are showing good correlation with Korsmeyer Peppas equation. n value of Korsmeyer Peppas equation lied within the range of 0.5-1 which shows that formulations show anomalous release. Among all the formulations formulated, batch F2 exhibit the best results. The response is due to their high entrapment efficiency, particle size, with better surface morphology and more sustained release than other microsphere formulation.

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CONFLICT OF INTERESTS: The authors declare that there is no conflict of interest.

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