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Formulation and Evaluation of Mesalamine Loaded pH Dependent Colon Specific Pulsatile Drug Delivery System

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ABSTRACT

The aim of these research of an oral colon specific, pulsatile device to attain time and or site specific release of Mesalamine, based on chronopharmaceutical consideration. The basic design consists of an insoluble hard gelatin capsule body, filled with Eudragit microcapsules of Mesalamine and sealed with a hydrogel plug. The entire device was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. The Mesalamine microcapsules were prepared in three batches, with Eudragit L-100 and S-100 (1:2) by changing drug to polymer ratio and evaluated for the particle size, drug content and *in vitro* release profile and from the obtained results; one better formulation was selected for further fabrication of pulsatile capsule. Different hydrogel polymers were used as plugs, to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. *In vitro* release studies of pulsatile device revealed that, increasing the hydrophilic polymer content resulted in delayed release of Mesalamine from microcapsules. Pulsatile, colon-specific release has been achieved from a capsule device over a 2–24 h period, consistent with the demands of chronotherapeutic drug delivery.

Key words: Mesalamine, Eudragit, microcapsules, Pulsatile, Colon-specific, Chronotherapeutics

1. INTRODUCTION

A pulsatile drug delivery system delivers drug in rapid and burst manner within a short time period immediately after a programmable lag phase. There are many situations where drug is needed to be released immediately (after bursting the delaying film coat) at specific site. Modified release dosage forms show different release profiles depending on their type. Sustain release dosage forms may maintain nearly constant plasma drug concentration in therapeutic window for prolonged time. Pulsatile release dosage forms release drug in pulsatile manner and maintain plasma drug level within therapeutic range. [3,5] Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers includes cellulose acetate phthalate, polyacrylates, sodium carboxymethylcellulose eudragit. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine. [17]

Colon-specific drug delivery systems (CDDS) is one of the site-specific drug delivery systems. Along with many applications in local and systemic delivery of drugs the CDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis.So by developing the pulsatile device for specific colonic delivery, plasma peak is obtained at an optimal time, number of doses per day can be reduced; saturable first pass metabolism and tolerance development can also be avoided.[15]

Modified-release oral dosage forms, increasing interest has presently turned to systems designed to achieve time specific (delayed, pulsatile) and site-specific delivery of drugs. These systems constitute a relatively new class of devices the importance of which is especially connected with the recent advances in chronopharmacology. In the last decade numerous studies in animals as well as clinical studies have provided convincing evidence, that the pharmacokinetics and/or the drug's effects-side effects can be modified by the circadian time and/or the timing of drug application within 24 h of a day On the other hand, colon-specific drug delivery systems (CDDS) have been developing as one of the site-specific drug delivery systems. Along with many applications in local and sys- temic delivery of drugs the CDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm. So by developing the pulsatile device for specific colonic delivery, plasma peak is obtained at an optimal time, number of doses per day can be reduced; saturable first pass metabolism and tolerance development can also be avoided. [9,11]

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The necessity and advantage of CDDS have been well recognized and reviewed recently There were currently few strategies to achieve colonic specificity such as bacterially triggered, pressure controlled, pH dependent and time dependent CDDS Recent studies with sensitive and reliable equipment contradict the traditional view and provide evidence of a decrease in pH at the gastrointestinal region between the ileum and the colon. Apparently the colon has a lower pH value (6.5) than that of the small intestine (7.0–7.8). Based on the concept that a formulation on leaving the stomach arrives at the ileocaecal junction in about 6 h after administration and difference in pH throughout GIT, a time and pH dependent pulsatile device proposed for colonic targeting was designed, for achieving the selective delivery of drugs to colon, which is a chronopharmaceutical approach for the better treatment of Hypercholesterolemia.[11] The designed capsule device consists of a non-disintegrating capsule body and a soluble cap. The microencapsulated drug formulation prepared by using pH sensitive methacrylic acid copolymers (Eudragit L-100 and S-100) as coat and Mesalamine as core material, is filled within the capsule body and separated from the water-soluble cap by a hydrogel plug. The entire capsule was enteric coated to prevent variable gastric emptying. The enteric coating prevents disintegration of the soluble cap in the gastric fluid. On reaching the small intestine, the capsule will lose its enteric coating and the water-soluble hydrogel polymer plug inside the capsule swells to create a lag phase that equals the small intestinal transit time. This plug ejects on swelling and releases the microencapsulated drug from the capsule in the colon. Further, the controlled release of Mesalamine was achieved for up to 24 h as it was microencapsulated in the pH sensitive polymer.[10,12]

Mesalamine is a member of the drug class known as statins. It is used for lowering cholesterol. Mesalamine inhibits the rate determining enzyme (HMG CoA reductase) located in hepatic tissue that produces mevalonate, a small molecule used in the synthesis of cholesterol and other mevalonate derivatives. This lowers the amount of cholesterol produced which in turn lowers the total amount of LDL cholesterol. Mesalamine is a competitive inhibitor of HMG CoA reeducates.cholesterol synthesis occurs during night time,especially it is higher at early morning. [13,14]

Hypercholesterolemia or high cholesterol occurs when there is too much cholesterol in the body cholesterol is soft, waxy, fat like substance natural component of all the cells of the body. Our body makes all the cholesterol its needs any added cholesterol, which comes from the food can cause harm. High cholesterol raises your risk for heart diseases, heart attack& stroke when their too much cholesterol circulating in the blood can create sticky deposit (called plaque) along the artery walls.[7]

A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutics system. Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastrointestinal motility, etc. Food has been shown to reduce the rate and extent of Mesalamine absorption. Administration of Mesalamine with food produces a 25% reduction in Cmax (rate of absorption) and a 9% reduction in AUC (extent of absorption). However, food does not affect the plasma LDL-C lowering efficacy of Mesalamine. Evening Mesalamine dose administration is known to reduce the Cmax (rate of absorption) and AUC (extent of absorption) by 30% each. Mesalamine undergoes high intestinal clearance and first-pass metabolism, which is the main cause for the low systemic availability. the colon specific delivery of Mesalamine can be avoid the first pass metabolism, So in present study Mesalamine has been found to be suitable drug candidate for the development of chronomodulated drug delivery. [4, 16]

2. MATERIALS AND METHODS

2.1 Materials

Mesalamine was obtained from MSN Pharma. pH sensitive methacrylic acid co-polymers (EudragitL-100 and S-100) were supplied as gifts samples matrix lab Ltd. Mumbai methanol is obtained from commercial supplier Hydroxypropylmethyl-cellulose-K4M (HPMC), Guar gum and sodium alginate were from

S.D. Fine Chem. Ltd., Mumbai. Cellulose acetate phthalate (CAP) for enteric coating was purchased from Rajesh Chemicals, Mumbai. hard gelatine capsules of 300mg capacity was obtained from Government collage of pharmacy, karad. The rest of the chemicals were obtained from the following commercial supplier and used as received without further purification: light liquid paraffin (loba chemicals), Span 80 (Research Lab. Mumbai), acetone, petroleum ether (S.D. Fine Chem. Ltd., Mumbai) were of analytical grade.

2.2 Method of Preparation

Accurately weighed Eudragit L-100 and S-100 in 1:2 ratios were dissolved in 10 ml of methanol to form a homogenous polymer solution. Core material, i.e. Mesalamine was dispersed in it and mixed thoroughly. This organic phase was slowly poured at 15°C into liquid paraffin (100 ml) containing 1%(w/w) of Span- 80 with stirring at 1000 rpm to form a uniform emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth-walled, rigid and discrete microcapsules were formed. The microcapsules were collected by decantation and the product was washed with petroleum ether (40–60 ◦C), four times and dried at room temperature for 3 h. The microcapsules were then stored in a desiccators over fused calcium chloride. Three batches were prepared with different proportions of core to coat materials (drug: polymer = 1:0.5, 1:0.75 and 1:1 (w/w) named AM-1–3, respectively). [1, 12]

2.3 Evaluation of microcapsules

2.3.1 Particle size and external morphology

Determination of average particle size of Mesalamine microcapsules was carried out by optical microscopy. SEM studies were carried out by using JEOL JSM T-330 A Scanning microscope (Japan). Dry microcapsules were placed on an electron microscope brass stub and coated with gold in an ion sputter. Picture of microcapsules were taken by random scanning of the stub.[10]

2.3.2 Drug content

` In a 100 ml volumetric flask, 30 mg of crushed microcapsules were taken, and volume was made up to mark withpH6.8. The flask was shaken for 12 h using an orbital shaker incubator. Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 240nm by using UV absorption spectroscopy. [1,2]

2.3.3 In vitro release studies

In vitro dissolution profile of each formulation was determined by employing USP XXIII rotating basket method (900 ml of pH 6.8-phosphate buffer, 100 rpm, 37±0.5 ◦C). Microcapsules equivalent to 40 mg of Mesalamine were filled into dialysis bags (12,000 molecular cut-offs) and loaded into the basket of the dissolution apparatus. Five millilitres of the sample was withdrawn from the dissolution media at suitable time intervals and the same amount was replaced with fresh buffer. The absorbance of the filtrate was determined at wavelength of 240 nm by using UV–vis spectrophotometer, against pH 6.8 as blank. The amount of drug present in the filtrate was then determined from the calibration curve and cumulative percent of drug release was calculate.[10]

Preparation of cross-linked gelatine capsules

`Twenty-five milliliters of 15% (v/v) formaldehyde was taken into desiccator and a pinch of potassium permanganate was added to it, to generate formalin vapors. The wire mesh containing the empty bodies of the 00 size hard gelatin (about100 in number) capsule was then exposed to formaldehyde vapors. The caps were not exposed leaving them water-soluble. The desiccator was tightly closed. The reaction was carried out for 12 h after which the bodies were removed and dried at 50OC for 30 min to ensure completion of reaction between gelatine and formaldehyde vapors. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated caps and stored in a polythene bag.[10]

2.3.4 Test for formaldehyde treated empty capsule bodies

Various physical tests such as, identification attributes, visual defects, dimension changes, solubility studies were carried out.[2]

2.3.5 Qualitative chemical test for free formaldehyde

Standard formaldehyde solution used is formaldehyde solution (0.002, w/v) and sample solution is formaldehyde treated bodies (about 25 in number) were cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 h with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50ml volumetric flask, washed with distilled water and volume was made up to 50 ml with the washings. In brief, to 1ml of sample solution, 9ml of water was added. One milliliter of resulting solution was taken into a test tube and mixed with 4ml of water and 5ml of acetone reagent. The test tube was warmed in a water bath at 40 ◦C and allowed to stand for 40 min. The solution was not more intensely colored than a reference solution prepared at the same time and in the same manner using 1ml of standard solution in place of the sample

solution. The comparison should be made by examining tubes down their vertical axis.[2]

2.3.6 *Formulation of pulsatile drug delivery system*

The bodies and caps of formaldehyde treated hard gelatine capsules of were separated manually. Microcapsules (AM-3) equivalent to 40mg of Mesalamine were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the microcapsules were then plugged with different amounts (20, 30 and 40 mg) of various polymers, i.e., guar gum, hydroxyl propyl methyl cellulose and sodium alginate. The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated by dip coating method with 5% CAP in 8:2 (v/v) mixture of acetone: ethanol, plasticized with dibutyl phthalate (0.75%), to prevent variable gastric emptying. Coating was repeated until an 8–12% increase in weight is obtained. % weight gain of the capsules before and after coating was determined which is shown in table no.1.

2.3.7 In vitro release profile of pulsatile capsule

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (paddle method). Capsules were tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float.In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used, referred to as sequential pH change method When performing experiments, the pH 1.2 medium was first used for 2 h (since the average gastric emptying time is 2 h), then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 h (average small intestinal transit time is 3 h), the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hours. Nine hundred millilitres of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5 ºC. Capsules were tied to paddle with a cotton thread in each dissolution vessel to prevent floating. Five millilitres of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 240nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.[12]

3. RESULT AND DISCUSSION

As indicated in introduction, the aim of the work described here was to design a new pulsatile, colonic drug delivery device, for the better treatment of Hypercholesterolemia. The pulsatile capsule designed here combines two approaches previously attempted: pH-sensitive delivery and time dependent delivery. The system was fabricated into two steps: first, Mesalamine was entrapped within pH dependent methacrylic acid copolymers (Eudragit L-100 and S-100 soluble at pH above 6 and 7, respectively); second, microcapsules were filled in non-disintegrating capsule body, and sealed with hydrogel plug and the entire capsule was coated with cellulose acetate phthalate for the enteric coating.

In case of Drug-Excipient compatibility study, it was observed that there were no changes in these main peaks in IR spectra of microcapsules, which show there were no physical interactions because of some bond formation between drug and polymers. The peaks obtained in the spectra of drug and polymers mixtures correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components. IR studies indicated no interaction between drug and polymers shown in figure no 1 and 2.

3.1 Physicochemical properties of eudragit microcapsules

To prepare pH dependent microcapsules the O/O (oil in oil) emulsion solvent evaporation technique was used since it yields more uniform particles. The method is correctly referred as O/O instead of W/O (water in oil) since a polymeric solution in organic solvent is considered as oil in microencapsulation terminology. The organic phase containing pH dependent Eudragit L/S-100 in combined ratio of 1:2 and dispersed Mesalamine was emulsified into an external oil phase. Liquid paraffin was used as the dispersion media or external phase. Petroleum ether was used to clean the microparticles since it removes liquid paraffin without affecting the integrity of the microparticles.

The arithmetic mean particle size of the formulations was determined by the optical microscope fitted with stage micrometer. The average mean particle sizes of the microcapsules were found to be 161.88, 183.45, and 238.10_µm for formulations AM-1, AM-2, and AM-3, respectively. The mean particle size of the microcapsules significantly increased with increase in polymer concentration due to high viscosity of medium at a higher polymer concentration resulting in enhanced interfacial tension and diminished shearing efficiency Scanning electron microscopy was performed to characterize the surface of the formed microcapsules. Particles of TM-1 were rough surfaced and crystals of the drug are visible on surface indicated that the concentration of polymeric solution is insufficient for complete encapsulation, whereas TM-2 is also rough but less crystalline as compared to TM 1.The TM-3 were found to be spherical, smooth and discrete. Some aggregates of polymer were found in TM-2. Scanning electron photomicrographs of all the three formulations are shown in Fig.2.

3.2 Percentage practical yields and drug content

The drug content was found to be high in all the cases probably due to polymer loss by adherence to the container as a result of viscous nature of slurry. Amount of microcapsules to be taken for *in vitro* release studies and further development of pulsatile capsule was calculated based on content of drug present in each formulation shown in table no.2.

3.3 *In vitro* release studies for microcapsules

In vitro release studies were carried out using USP XXIII dissolution assembly. The release profile obtained for all the Three formulations were shown in Fig. It was observed that the drug release from the formulations decreased with increase in the amount of polymer added in each formulation The release of drug from polymer matrix takes place after complete swelling Comparative *in vitro* release profiles for the Eudragit microcapsules.

Results shown are mean of three experiments, errorbars omitted for clarity,of the polymer and as the amount of polymer in the formulation. increase the time required to swell also increase thereby decrease in the drug release. In the first two hour drug release was 38.76%, 37.69%, and 31.05% for AM-1, AM-2 and AM-3, respectively. The overall cumulative % release for AM-1, AM-2, and AM-3 wereNfound to be 95.76%, 92.87%, and 91.13% at the end of 12th hour. . shown in figure no 6.

In vitro release study was analyzed using various mathematical models. The regression coefficients for formulation AM-1 to AM-3 of zero-order plot were found to be 0.946, 0.914 and 0.960, respectively. The regression coefficients for formulations AM-1–3 of first-order plot were found to be 0.578, 0.557 and 0.599, respectively. Higuchi matrix plot regression coefficients of formulations AM-1–3 were found to be 0.983, 0.968, and 0.973, respectively. The regression coefficients for formulations AM-1–3 of Hixson Crowell plot were found to be 0.677, 0.618, and 0.648 respectively. The regression coefficients for formulations AM-1–3 of korsmeyer peppas plot were found to be 0.766, 0.724, and 0.746 respectively which is shown in figure no 6.

3.4 Formaldehyde treatment of hard gelatin capsule

Formalin treatment has been employed to modify the solubility of the gelatin capsules. Exposure to formalin vapors results in an unpredictable decrease in solubility of gelatin owing to the cross-linkage of the amino groups in the gelatin molecular chain with aldehyde groups of formaldehyde by Schiff's base condensation. In about 100 capsule bodies treated with formaldehyde, about ten were found to be shrunk or distorted. Capsule of 100 mg capacity showed a significant decrease in length and diameter after treatment. The solubility tests were carried out for normal capsules and formaldehyde treated capsules for 24 h. It was observed that in all the case of normal capsules, both cap and body dissolved within 15 min where as in formaldehyde treated capsules, only the cap dissolved within 15 min, while the capsule body remained intact for about 24 h and hence indicates the suitability for colon targeting.

3.5 Evaluation of modified pulsatile capsule

On the basis of drug content, particle size morphology, *in vitr*o release and release kinetics, formulation AM-3 was selected as better formulation for designing pulsatile device. *In vitro* release profiles of pulsatile device during 24 h studies were found to have very good sustaining efficacy. The results obtained for all the nine formulations (F1–F9) are shown in Fig., indicating The plots of comparative *in vitro* release profile for formulation F1–F3 (a), F4–F6 (b) and F7–F9 (c), which contains guar gum, sodium alginate and HPMC respectively as hydrogel plugs at different proportions. During dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 h in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4, then the exposed polymer plug absorbed the surrounding fluid, swelled and released the drug through the swollen matrix. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the eudragit microcapsules into simulated colonic fluid (pH 6.8 phosphate buffer). With all the formulations, there was absolutely no drug release in pH 1.2, thus indicating the efficiency of 5% CAP for enteric coating.

3.6 Formulations with guar gum as hydrogel plug

With formulations F1 (20 mg), F2 (30 mg), at the end of 5^{th} there was 6.47% and 4.25% cumulative drug release was found In case of F1 and F2 it was observed that polymer concentration was sufficient to retard the drug release in small intestinal fluid and the plug ejected out in colonic fluid, releasing the entire drug in colonic pH, in a controlled manner. At the end of 24 h, 93.55% and 95.02% of drug release was found in F1 and F2,respectively. With F3, a decrease in expelling power of plug was observed which might be due to inadequate wetting of the polymer. It was observed that plug ejected after 6 h and at the end of 24 h 87.94% of drug release was observed shown in figure no.7

3.7 Formulations with sodium alginate as hydrogel plug

With formulation F4 (20 mg), F5 (30 mg), at the end of 5^{th} hour 8.91% and 7.36% of drug was released respectively and at the

end of 24th hour F4 formulation had released 95.97% of drug, whereas F5 formulation released 90.16% of drug up to 24 h in controlled manner. In case of F6 (40 mg), hydrogel plug ejected out in between 6th and 8th hour, indicating decrease in expelling power of plug. At the end of 24th hour 88.61% of drug was released shown in figure no.8.

3.8 Formulation with HPMC as hydrogel plug

`With formulations F7 (20 mg), F8 (30 mg) and F9 (40 mg),at the end of 5th hour around 7.03%, 5.92%, 4.49% of drug release was observed respectively. F7 released 91.24% of drug within 20 h where as F8 and F9 released 90.57% and 84.84% of drug at the end of 24th hour. shown in figure no.9

4. CONCLUSION

The present investigation demonstrates that the Mesalamine microcapsules could be successfully colon targeted by design of time and pH dependent modified chronopharmaceutical formulation. In conclusion, pulsatile drug release over a period of 2–24 h, consistent with the requirements for chronopharmaceutical drug delivery was achieved from insoluble gelatin capsules, in which microencapsulated Mesalamine was sealed by means of a suitable hydrogel plug, thus allowing pulsatile and in the case of gastro resistant systems, colon-specific drug delivery to be attained. Thus the designed device can be considered as one of the promising formulation technique for preparing colon-specific drug delivery systems and hence in chronotherapeutic management of hypercholestromia is done.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

Table 1. Composition for modified pulsatile device on the basis of design summary

Batch code	Weight of empty body (mg)	Weight of Microcapsules (mg)	Polymer used	Weight of polymer used (mg)	Total weight with cap (mg)	Weight after cap coating (mg)
F1	60	84	Guar gum	20	184	200
F2	60	84	Guar gum	30	194	210
F3	60	84	Guar gum	40	204	225
F4	60	84	Sod. Alg.	20	185	200
F5	60	84	Sod. Alg.	30	197	215
F6	60	84	Sod. Alg.	40	207	225
F7	70	84	HPMC	20	184	200
F8	70	84	HPMC	30	195	210
F9	60	84	HPMC	40	200	220

HPMC: hydroxy propyl methylcellulose; Sod. Alg.: sodium alginate. Microcapsules equivalent to 40 mg of drug used

Table 2. Results of drug content for Mesalamine microcapsules

Formulation	Absorbance	Concentration (g/ml)	Practical drug content (g/ml)	Theoretical drug content (g/ml)	%Drug content
AM 1	0.511	16.69	83.48	20	83.48
AM 2	0.483	15.79	92.14	17.14	92.14
AM 3	0.438	14.34	95.60	15	95.60

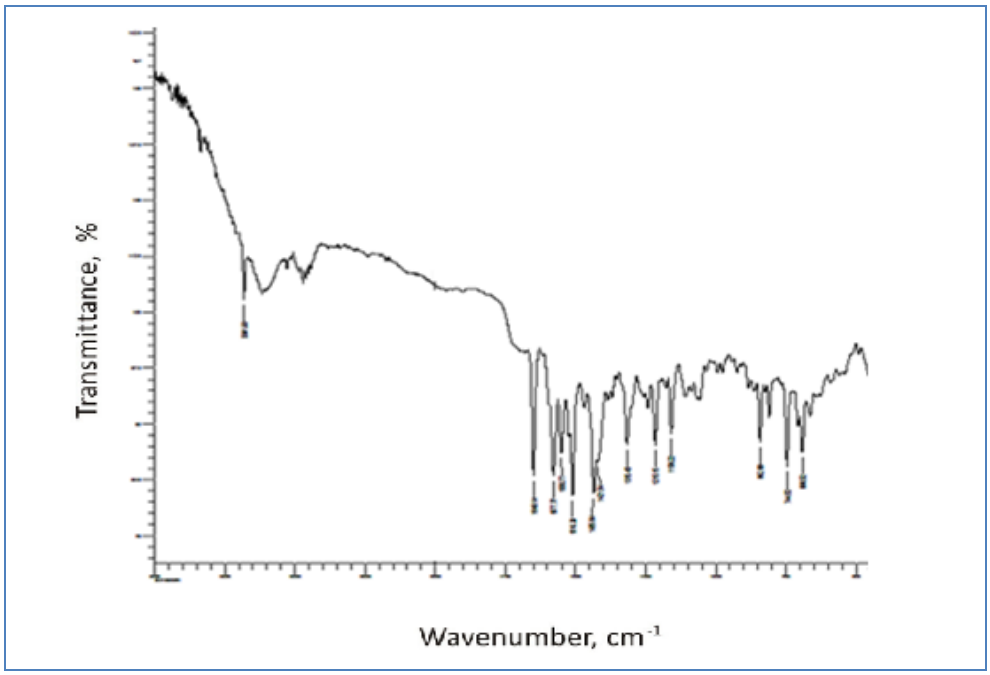


Fig. 1. : IR spectra of pure Mesalamine

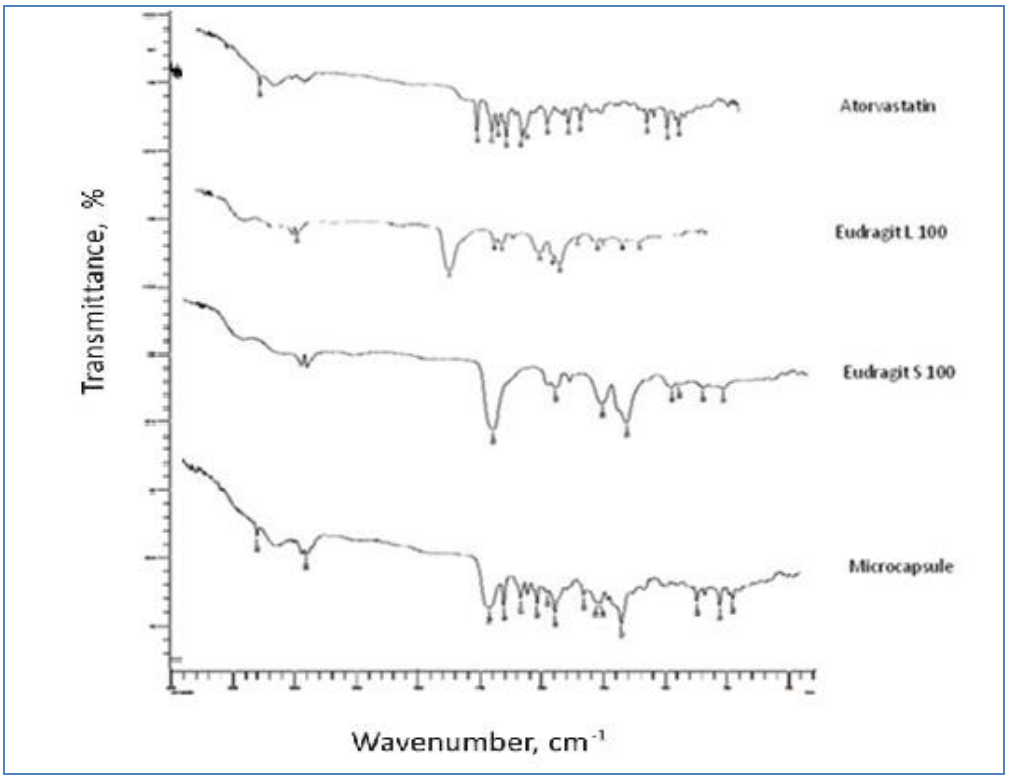
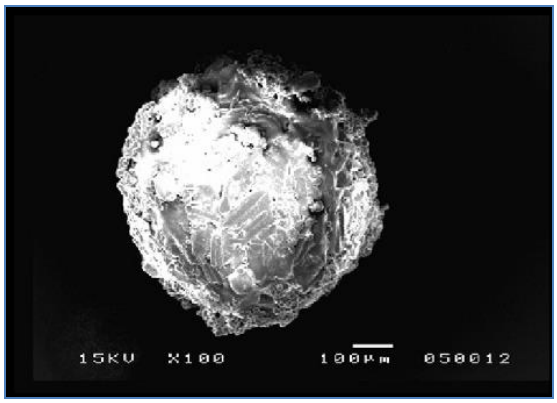


Fig. 2: IR Spectra of Mesalamine, Eudragit L100,Eudragit S 100 and Microcapsule



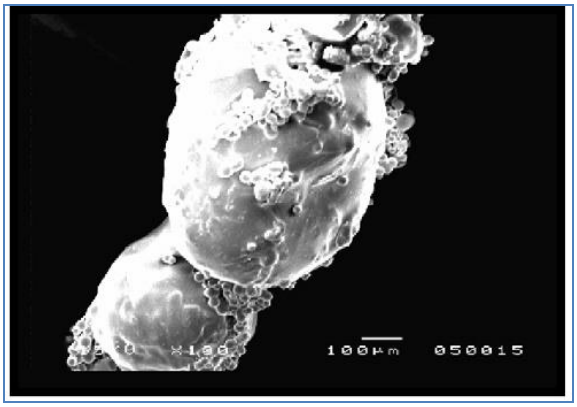


Fig.3 & 4. Scanning electron micrographs of theophylline microcapsules for AM 1 formulations

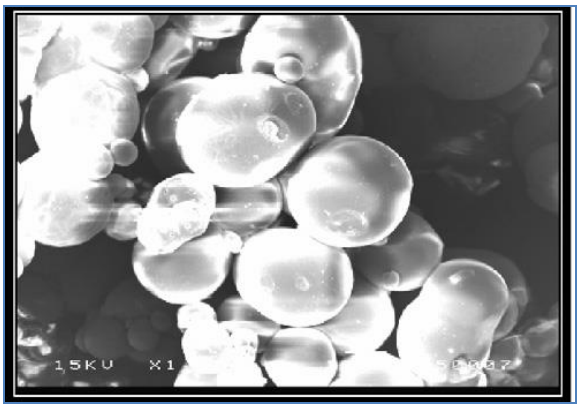


Fig. 5. Scanning electron micrograph of AM 3

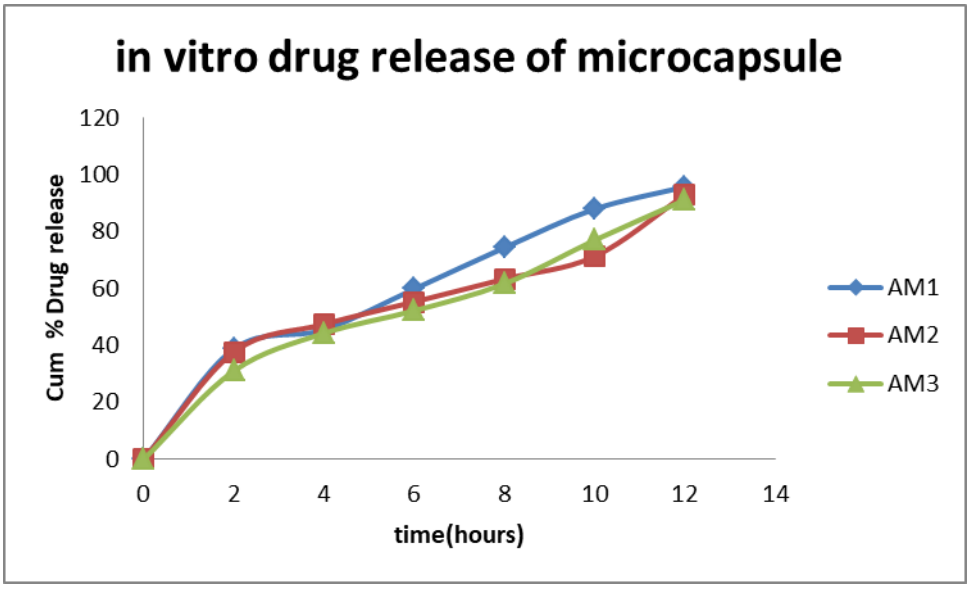


Fig. 6. Comparative *in vitro* release profiles for the Eudragit microcapsules

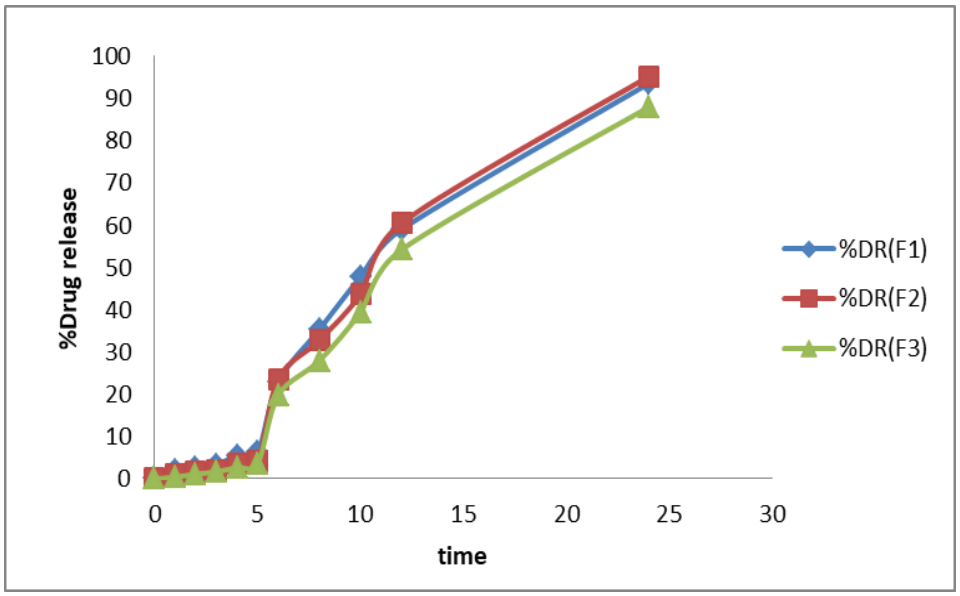


Fig. 7. Comparative *in vitro* release profile of formulations F1, F2, F3

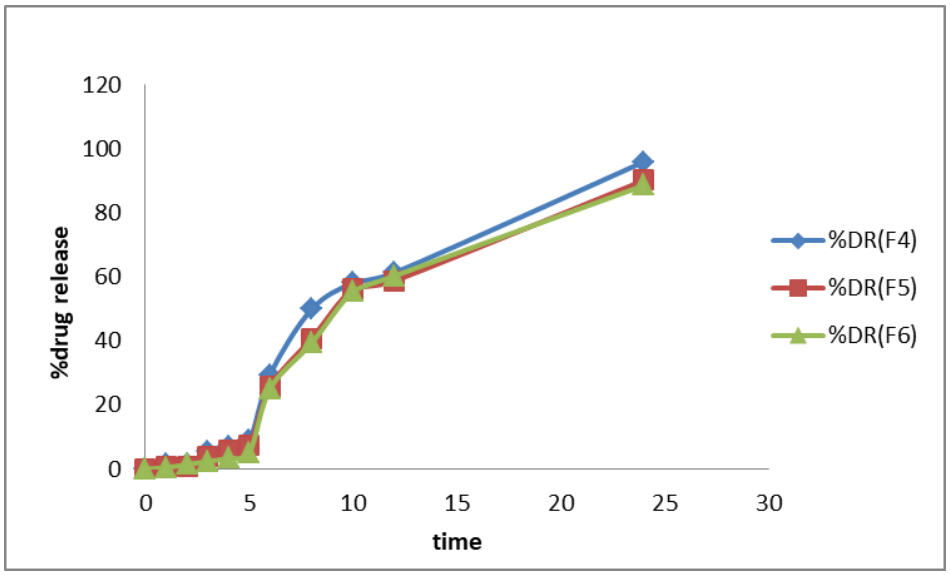


Fig. 8. Comparative *in vitro* release profile of formulations F4, F5, F6

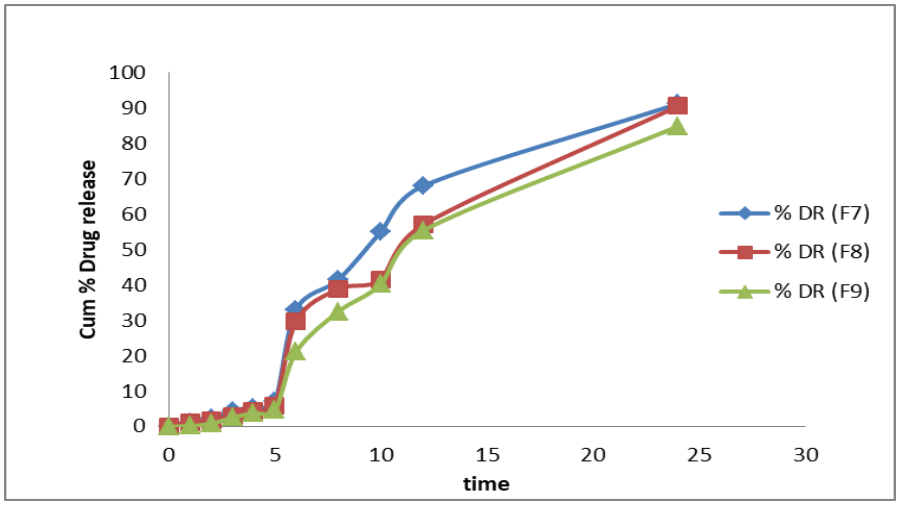


Fig. 9. Comparative *in vitro* release profile of formulations F7, F8, F9

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