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Design and Evaluation of Delayed and Extended Release Tablets of Mesalamine

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Abstract

The present study was focused on optimization of the formulation for the delayed and extended release tablets of mesalamine. Various formulations was prepared by wet granulation technique using the polymers, such as HPMCK-100M, HPMC K4M, HPMCE15 and HPMC E5. It was found that the best formulation ML10 showed 98.75 % of drug release at the end of 10 th hour. This way the best formulation was achieved by using the combination of high and low viscous polymers HPMC K4M and HPMC E5 in the ratio of 60:40 was able to prolong the drug release for about 10 hrs in pH 7.5 phosphate buffer. In-vitro drug release studies of mesalamine delayed and extended release tablets showed that, the rate of the drug release follows first order kinetics as indicated straight line with good correlation coefficient for the plot of log percentage drug remaining vs time. The rate of drug release was found to be dissolution control as there was a good correlation coefficient for the plot of Hixon-Crowell cube–root law.

Keywords: Mesalmine, deayled, extended, tablets, kinetics, correlation coefficient.

Introduction

An ideal drug delivery system should fulfill two prerequisites. The first is to deliver the drug at a rate dictated by the needs of the body over the period of treatment and the second is spatial targeting to specific sites. These prerequisites provide a need for modified release technologies, which can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, there by reducing both the size and number of doses required (1) Modified release dosage forms can be defined as one for which the release characteristics of time course and location are chosen to accomplish therapeutic or convenience objectives, which are not offered by conventional dosage forms (2) Most modified release products are orally administered tablets and capsules. Several types of modified release dosage forms are available.

They include: Extended release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time after administration of a single dose. Extended release dosage form allows at least two fold reduction in dosage frequency as compared to that drug presented in immediate release dosage forms. Ex: controlled release, sustained release. Delayed release dosage form is designed to release the drug at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions, like gastrointestinal pH. Ex: enteric coated dosage forms. Repeat action forms usually contain two single doses of medication, one for immediate release and the second for delayed release**.**

Targeted release describes drug release directed towards isolating or concentrating a drug in a particular body region, tissue or site for absorption or for drug action.

The advantages of extended release dosage forms over conventional forms [2] include the less fluctuation in drug blood levels, frequency reduction in dosing, enhanced convenience and compliance, reduction in adverse side effects and reduction in overall health care costs. The rate of drug release from solid dosage form may be modified by the

technologies, which in general are based on modifying drug dissolution by controlling access of biologic fluids to the drug through the use of barrier coatings, Controlling drug diffusion rates from dosage forms and chemical reaction or interaction between the drug substance or its pharmaceutical barrier and site specific biological fluids. Generally the different techniques (3) employed to fabricate the modified release dosage forms are coated beads, granules and microspheres, multi tablet system, micro encapsulated drug, complex formation, ion exchange resins, and embedding drug in slowly eroding or hydrophilic matrix system.

In delayed release dosage forms (4) generally enteric coating is used to protect the drugs (digoxin and erythromycin) from the gastric acidic environment, to prevent or reduce the side effects of drug by protecting the gastric mucosa from some drugs (indomethacin), to deliver some drugs intended for local action in the intestine, for example intestinal antiseptics can be delivered to the site of action in concentrated form and avoid stomach absorption and to provide a delayed release component for repeat action tablets.

The use of polymeric matrix devices to control the release of a variety of therapeutic agents has become increasingly important in the development of modified release dosage forms (5). A matrix device is a drug delivery system in which the drug is dispersed either molecularly or in particulate form within a polymeric network. This device may be a swellable, hydrophilic monolithic systems, erosion controlled monolithic systems or non erodible systems (6). The hydrophilic gel forming matrix tablets are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity due to dose dumping (7).

Mesalamine is mainly used in the treatment of ulcerative colitis, is a form of inflammatory bowel disease (IBD). Inflammatory bowel disease including irritable bowel syndrome, ulcerative colitis, and Crohn's disease are considered as serious colonic disorders. Ulcerative colitis is a chronic, lifelong, recurrent disease characterized by inflammation of the colorectal mucosa and characteristic ulcers or open sores in the colon. In the United Kingdom, the annual incidence is around 7 cases per 100,000 populations (8). Ulcerative colitis if not treated, leads to colon cancer. More than 66.000 cases of colon cancer are reported to occur every year in India. Cancer of the large intestine accounts for about 15% of cancer deaths in India (9).

Materials and Methods

Mesalamine was obtained as a gift sample from Dr.Reddy's LtD, Hyderabad. The polymers such as Hydroxypropyl methyl cellulose (E5), HPMC(K100M) and HPMC (E15) respectively from Dow chemicals, USA and HPMC (K4M) from colorcon Asia Ltd. Aerosil, Talc and Magnesium sterate from Imifab USA.

Formulation

The active ingredient was sifted through sieve #20 and all other ingredients except lubricant material were sifted through sieve #20 followed by the lubricant material was sifted through sieve#40. Then the active pharmaceutical ingredient and the intragranular materials were loaded in a double cone blender and mixed for 15 min. Using a granulating agent the dry mix was granulated and granulation was done till it forms uniform granules. The wet granular mass of the above step was taken in to a rapid air dryer. Then the wet mass was dried at an inlet temperature of 60± 5^0C and LOD of the dried granules should not be more than 3%. Then the dried granules were sifted through sieve # 20. The sifted granules and the sifted extra granular material were loaded in to the double cone blender. They were mixed for 5 min. and the blend was charcterised for the different physical parameters such as bulk density, Tapped density, Angle of repose, Hausners ratio and Carr,s index.

The prepared blend was compressed into tablets by using 16-station Cadmach rotary press. In this machine the hopper holds the granular blend. When the head of the rotary tablet press rotates, the punches are

guided up and down by fixed camtracks, which control the sequence of filling, compression and ejection. When the granule empties in to the feed frame, the pull-down camtrack allows the dies to overfill. While rotating, a wipe-off blade at the end of feed frame removes the excess granulation and the upper punch enter a fixed distance in to the dies and compact the granules within the dies. Then the lower punches ride up the cam to bring the tablets slightly above the surface of the dies. Weight and hardness of the tablets was fixed as per specifications during compression and the evaluation of physical parameters of the tablets was done.

Dissolution studies

Invitro dissolution studies were carried out for the tablets using U.S.P dissolution apparatus II (paddle type) and the conditions were specified in the Table.1 and Table.2. In the test procedure 900 mL of dissolution medium (0.1N HCl) was transferred in to vessels of dissolution tester and was allowed to reach the temperature of 37±0.5^{0}C. Preweighed tablets were rapidly placed in to the vessels and test was started. Samples were withdrawn at 1st h and 2nd h. then the solution was filtered through a 0.45 μm pore filter. The tablets were taken out at the end of 2nd h and were placed in the dissolution medium of pH 6.8/ 7.5 Phosphate buffer, which was already equilibrated to 37^{0}C. Samples were collected at 1 h interval for about 10 h. The absorbance was determined using the UV/Visible spectrophotometer at the wavelength of 330 nm, after filtration through 0.45 μm pore filter.

***Invitro* dissolution studies of the enteric coated tablets:**

Invitro dissolution studies of the enteric coated tablets were carried out in 0.1 N HCl for about 2 h and then the tablets were transferred to pH 7.5 phosphate buffer and the dissolution study was carried out for about 10 h. Three trials were performed.

Delayed released coating:

Mesalamine is used in the treatment of ulcerative colitis. This drug is intended for local action in the colon, so delayed release coating is required to prevent the drug release in acidic conditions of the stomach. Eudragit L100 was used as an enteric coating material. This material was able to release the drug above pH 6. If there is any inflammation in the intestine that will also be cured with the drug, which is releasing in the intestine and the drug, which is released in the colon, will reduce the inflammation in the colon part. The composition of the coating solution is given in the Table.3

Preparation of coating solution:

Eudragit L100 was dissolved in a solution of 450 g of IPA and 225 g of water with the help of stirrer. Triethyl citrate and talc was dissolved in the remaining amount of isopropyl alcohol with the help of homogenizer. The solution of step 2 was added to Eudragit L100 solution.

Application of coating solution:

Mesalamine extended release core tablets were prepared as per the optimized formulation ML10 and delayed release coating was applied to the tablets as per the specifications mentioned above. The prepared tablets are placed in Gansons coating machine. The enteric coating solution was applied on to the tablets at the spray rate of 1 rpm and the pan speed was adjusted to 7 rpm. Inlet and outlet temperatures of 40°c and 33-34°c respectively with atomization of 1-2Kg/cm^2. Coating solution was applied till the tablet weight rises to 5-6 % of initial tablet weight. Finally the tablets were allowed to dry in the coating machine by stopping the application of coating solution and by reducing the pan speed.

Results and discussion

The first trial ML1 was carried out as per multi matrix technology by using hydrophobic and hydrophilic polymers in intra and extra granular parts of the formulation. Bulk density and tap density and other blend characteristics were evaluated. Physical parameters of the tablets and *in vitro* dissolution studies were carried out. It was found that 27.5% drug was released at the end of 7th hour (Fig.1) which may be due to the use hydrophobic polymer in intra granular part of the formulation.

Table. 1 Dissolution test conditions in 0.1 N HCl

Parameter	Specification
Dissolution medium	0.1N HCl
Volume of medium	900 mL
Temp. of medium	37±0.5^{0}C
Paddle rotation speed	50 rpm
Sampling time interval	1h, 2h
Detection wavelength	330 nm

Table. 2 Dissolution test conditions in phosphate buffer

Parameter	Specification
Dissolution medium	PH 6.8 / 7.5 phosphate buffer
Volume of medium	900 mL
Temp. of medium	37±0.5 ^{0} C
Paddle rotation speed	100 rpm
Samping time intervals	For every h. up to 10h
Detection wavelengh	330 nm

The second trial ML2 was carried out to improve drug release profile by omitting the hydrophobic polymer Ethyl cellulose and poly vinyl pyrrolidine from the formulation. The granular properties of the blend were found to be satisfactory and the granules showed excellent flow properties. Capping was observed when the hardness was increased above 13 kp. All other physical parameters were found to be with in the acceptable range.

Table.3 Coating solution composition

Material	Quantity (g)
Eudragit L100	63
Triethyl citrate	6.3
Talc	14.7
Isopropyl alcohol	q.s (675g)
Purified water	q.s(225g)

Table.4 Preformulation parameters of the blend

S.No.	PARAMETER	RESULT
1	Bulk density	0.576 g/mL
2	Tapped density	0.681 g/mL
3	Compressibility index (%)	17.3
4	Hausner's ratio	1.18
5	Angle of repose	21.9±0.8°

Table. 5 Physical parameters of tablets

Parameter	RESULT		
	Maximum	Minimum	Average
Weight (g)	1.414	1.401	1.406
Thickness (mm)	6.95	6.93	6.94
Hardness (kp)	19.7	18.6	19.06
Friability	0.176%		
Weight variation	-0.355 to 0.568		
Assay	97.9%		

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Weight variation	-0.355 to 0.568		
Assay	97.9%		

Figure. 1. Dissolution profile of ML1

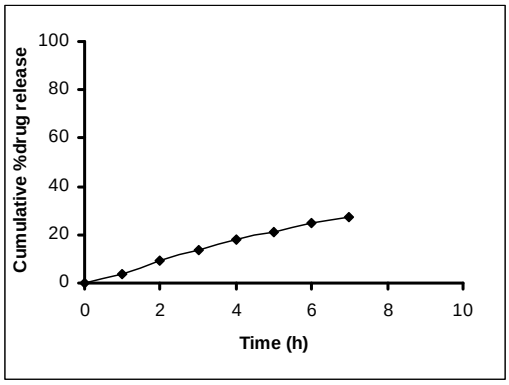


Figure. 2. Dissolution profile of ML2 tablets

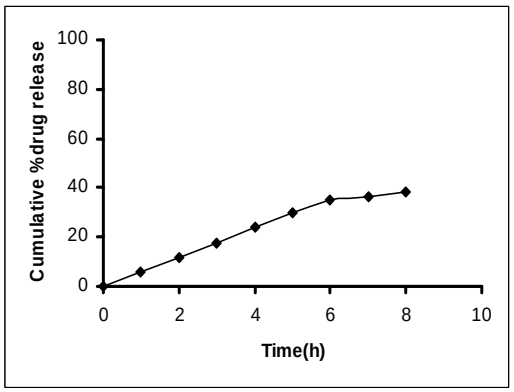


Figure. 3. Dissolution profile of ML4

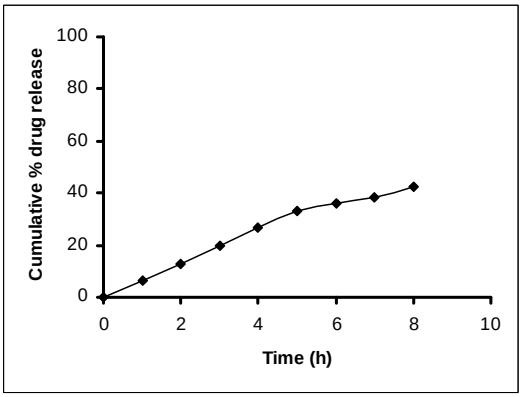


Figure. 4. Dissolution profile of ML5

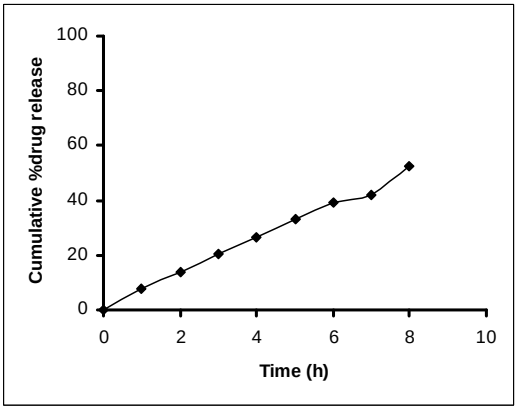


Figure. 5. Dissolution profile of ML6

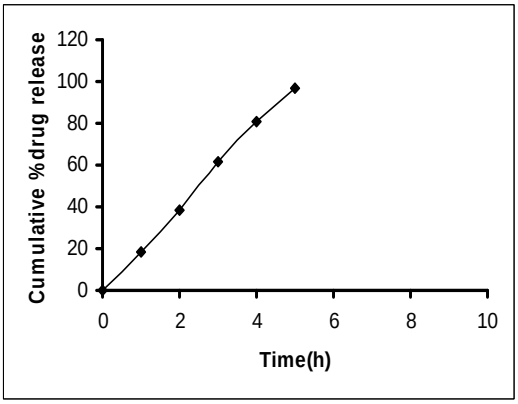


Figure. 6. Dissolution profile of ML8

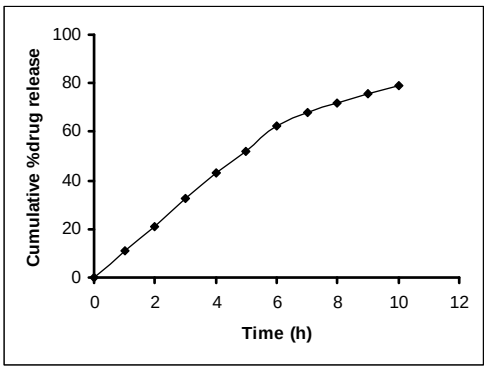


Figure. 7. Dissolution profile of ML8

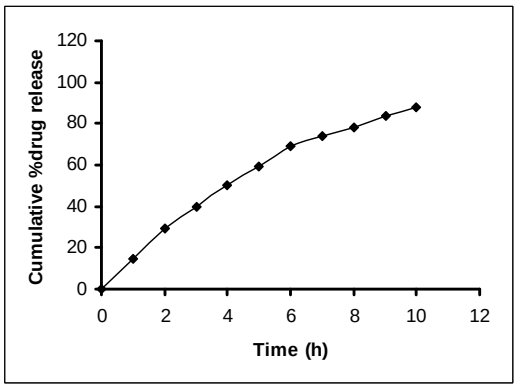
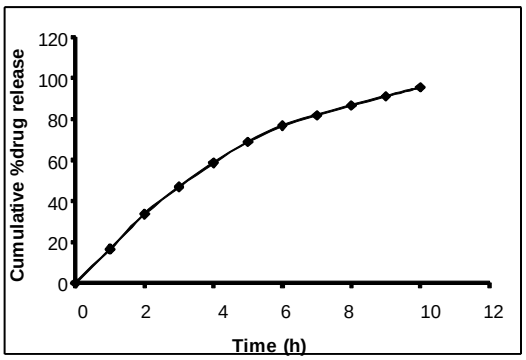


Figure 8. Dissolution profile of ML9



38.6% of the drug was released at the end of 8th hour (Fig.2).

Next trail ML3 was carried out to further improve the drug release profile by replacing the high viscous polymer HPMC K15 M with a low viscous polymer HPMC E15. The granules showed excellent flow properties. Capping problem was existed during the compression. Dissolution studies were not

Figure. 9. Dissolution profile of ML10

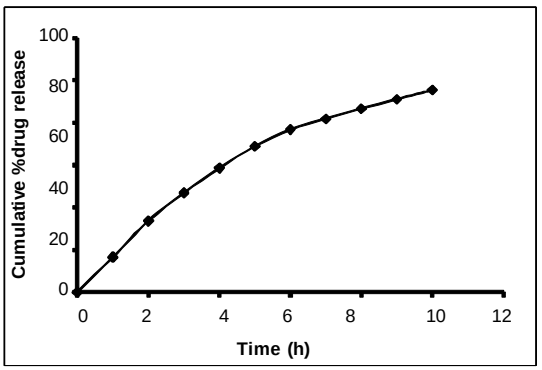
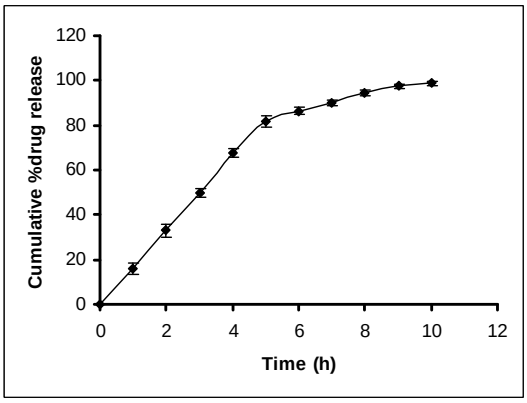


Figure. 10. Dissolution profile of enteric coated tablets



carried out due to the problem of capping. Fourth trial ML4 was carried out with the aim of controlling the problem of capping by using PVP K30D as a binder to improve the drug release profile by removing the intra granular polymer. All the granular properties were found to be satisfactory and the granules showed excellent flow properties. Capping was still observed when the hardness was increased. Desired drug release was not achieved as only 42.3% drug was found to be released at the end of 8th hour which may be because of high viscous extra granular polymer (Fig.3).

Further trial ML5 was carried out by completely omitting extra granular polymer HPMC K100 M and by using HPMC K15M only in intra granular part of the formulation. The granules showed excellent flow properties. Capping problem was still seen

Table. 6 Comparison of order of release of Mesalamine

Model	Zero order (r values)	First order (r values)	Higuchi model (r values)	Hixson - Crowell (r values)
Mesalamine core tablet	0.892	0.9648	0.9663	0.9959
Enteric coated tablet	0.8989	0.9721	0.9574	0.9948

when hardness was increased above 13 kp. The drug release was found to 52.74% at the end of 8th hour (Fig.4). Sixth trial ML6 was carried out to check the ability of aerosol to control the problem of capping and to further improve the drug release profile by using a low viscous polymer HPMC E15M. Tablets did not show capping up to the hardness of 20kp which may be due to the aerosol. From the dissolution studies it has been observed that the drug release was 96.55% with in 5th hour which may be due to the usage of low viscous polymer (Fig.5).

Another trial ML7 was carried out to prolong the drug release for 10 hrs by replacing HPMC E15M with a high viscous polymer HPMC K4M in intra granular part of the formulation. Desired drug release was not achieved as only 79% release was observed at the end of 10th hour. Drug release may be retarded by the polymer HPMC K4M (Fig.6). Eighth trial ML8 was carried out to improve the drug release profile by using a combination of polymers HPMC K4M and HPMC E15M in the ratio of 80:20. Drug release was found to be improved up to 87.9% in 10th hour (Fig.7). Ninth trial ML9 was carried out to improve the drug release profile by increasing the ratio of low viscous polymer to 30%. Drug release was found to be improved up to 94.2% in 10th hour (Fig.8). Tenth trial ML10 was carried out to improve the drug release profile by increasing the ratio of low viscous polymer to 40%.Granular properties were found to be satisfactory (Table.1). Physical parameters were found to be with in the acceptable range (Table.2).Desired drug release of 98.9% was achieved at the end of 10th hour (Fig.9)

The optimized formulation which is capable of releasing the required quantity of drug at the end of tenth hour was used in the preparation of core tablets. The delayed release coating was applied to the optimized core tablets to prevent the drug release in the acidic conditions of the stomach. Eudragit L100 was used as an enteric coating polymer it was found that less than 1% of drug was released in acidic conditions in first two hours. Where as 98.7% drug was found to be released in pH 7.5 phosphate buffer in 10 hours which is desirable (Fig.10).

Comparison of order of drug release of mesalamine delayed and extended release tablets is given in Table.6.Graph of cumulative % drug release versus time resulted in straight line with r = 0.8989 . Graph of log % drug remaining versus time showed a linear relationship with r = 0.9721. The correlation coefficients obtained for first order plot was found to be superior on comparison with r values of zero order plots. Therefore, it is concluded that the release of mesalamine follows first order. Graph of cumulative % drug release versus square root of time the resulted in straight line, with r= 0.9574. The Graph of the $M_0^{1/3} - M^{1/3}$ versus time showed a linear relationship with r = 0.9948. The correlation coefficients obtained for Hixson- Crowell cube root plot was found to be superior on comparison with r values of Higuchi plot, indicating that the release of mesalamine was dissolution controlled. Further, the correlation coefficient value of first order plot for mesalamine core tablet was found to be 0.9648, where as for enteric coated tablet r = 0.9721. From the results, it

can be concluded that the core tablet does not change its release pattern after coating.

Conclusion

The objectives of the present study were successfully met by step wise optimization of the formulation. The results generated from these studies form strong base for the large scale production of the product. The best formulation M10 was achieved by the combination of high and low viscous polymers such as HPMC K4M and HPMC E 15 in the ratio 60:40 was able to prolong the drug release for about 10 hrs in pH 7.5 phosphate buffer.

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