FORMULATION AND EVALUATION OF MESALAMINE DELAYED AND EXTENDED-RELEASE TABLETS

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Abstract

Mesalamine is an anti-inflammatory drug used in the treatment of inflammatory bowel diseases. In order to exhibit therapeutic properties, the drug should be available in colon over an extended time period. In the present investigation, an attempt was made to formulate delayed and extended-release drug delivery system which reduces the dosing frequency by developing delayed and extended-release tablets of mesalamine. To achieve this, formulated drug product should bypass stomach (Delayed release) using enteric polymers and show hindrance in drug release (Extended release) using rate controlling polymer over an extended period of time.

Methocel E 50 (Low viscous grade) used as a binder due to its low viscous property, HPMC K4M (High viscous grade) as a release retardant due to its high viscous property in different proportions and sodium CMC as a super disintegrant to achieve desired drug release to formulate an extended release core part using wet granulation technique and to attain delayed release property Eudragit S 100 and Eudragit L 100 are used as an enteric coating polymers and evaluated in different PH conditions to observe drug release profile such as Acid stage: 100mM HCL 750 ml for 2 hrs followed by Buffer stage I: PH 6.4 phosphate buffer 950 ml for 1 hr followed by Buffer stage II: PH phosphate buffer 960 ml for 1,2,4,6,8 hrs and infinity and , formulated test drug products are compared with innovator drug product and formulation 9 was found to be optimized .

Keywords

Delayed release, Extended release, Mesalamine.

1) Introduction

An ideal drug delivery system should full fill 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, thereby 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.

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.

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).

2) Materials and Methods

Mesalamine was obtained as a gift sample from IpcaLaboratoriesltd., Mumbai. The polymers and other excipients such as Microcrystalline cellulose (Avicel pH 101), Colloidal silicon dioxide, Sodium CMC, Crospovidone, Methocel (Low viscous grade), HPMC (High viscous grade), from SD Fine chemicals PEG 6000, Magnesium stearate (Hi media Laboratories), Eudragit S100, Eudragit L100 (Evonik), Talc, Titanium dioxide and Red Ferric Oxide were purchased from Colorcon Pvt.Ltd.

2.1)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 50 C 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. Dissolve Methocel in water and IPA mixture under continuous stirring, the proportion of water to IPA is 70:30 parts. (Binder solution for formulations F1, F2, F3 and F4.)

Next added slowly the weighed quantity of Methocel to purified water under continuous stirring until no observation of lumps in the solution and let it be free of foam. (Binder solution for formulations F5, F6, F7, F7A, F8 and F9.)

They were characterised for the different physical parameters such as bulk density, tapped density, Angle of repose, Hassner's ratio and Carr's index. The prepared blend was compressed into tablets by using 16-station Cad Mach 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 Cam tracks, which control the sequence of filling, compression and ejection. When the granule empties in to the feed frame, the pull-down Cam track 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.

2.2) DISSOLUTION PROCEDURE (DRUG RELEASE BY U.V) FOR MESALAMINE TABLETS, 1.2 g (INNOVATOR AND TEST DRUG PRODUCTS):

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 6.4/ 7.2 Phosphatebuffer, which was already equilibrated to 37^0 C. Samples were collected at 1 h interval for about 8h and infinity. The absorbance was determined using the UV/Visible spectrophotometer at the wavelength of 330 nm, (For acidic samples measured the absorbance at 298 nm.)after filtration through 0.45 µm pore filter.

2.3) IN-VITRO 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 7.2 phosphate buffer and the dissolution study was carried out for about 8 h. Three trials were performed

PREPARATION OF COATING SUSPENSION

Specified quantities of enteric polymers Eudragit S 100 and Eudragit L 100 were dissolved in each respective formulation in IPA under constant stirring (solution I) .Then dissolved poly ethylene glycol of each respective formulation in purified water under continuous stirring and add it to the solution I. (solution II) Plasticizer were added (diacetylated mono glyceride for formulations F1, F2, F3, F4 and tri ethyl citrate for formulations F5, F6, F7, F7 A, F8 and F9) to solution II.(solution). The remaining ingredients of enteric coating stage of each respective formulation were dispersed in IPA under continuous stirring and homogenize the dispersion for 45 minutes. Add this dispersion to solution III. (Final coating suspension)

COATING

Enteric coating of the core tablets with the enteric coating suspension under suitable process conditions to achieve a desired enteric coated tablet weight of each respective formulation.

The prepared tablets are placed in Neo machinescoating machine. The enteric coating solution was applied on to the tablets at the spray rate of 6-9 rpm and the pan speed was adjusted to 5-8 rpm. Inlet and outlet temperatures of 40°c and 33-34°c respectively with atomization of 1-2Kg/cm2. 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.

3) RESULTS AND DISCUSSION:

GRANULATIONPARAMETERS:

FORMULATION	IMPELLERRPM	CHOPPERRPM
DRYMIXSTAGE		
F1–F9	150 – 180	NIL
BINDERADDITIONSTAGE		
F1	150	NIL
F2	175	NIL
F3	250	500
F4	250	850
F5	250	800
F6	250	500
F7,F7A	250	500
F8	250	500
F9	180	1800

TABLE2: COATING PARAMETERS	
Inlet temperature	35-40 ^{0} C
Product temperature	30-33 ^{0} C
Pan RPM	5 – 8 RPM
Spray pump RPM :	6 - 9 RPM
Atomization air	1.8Kg/cm^2
Time taken for coating	3 hrs (approximately

Dissolutionparameters:

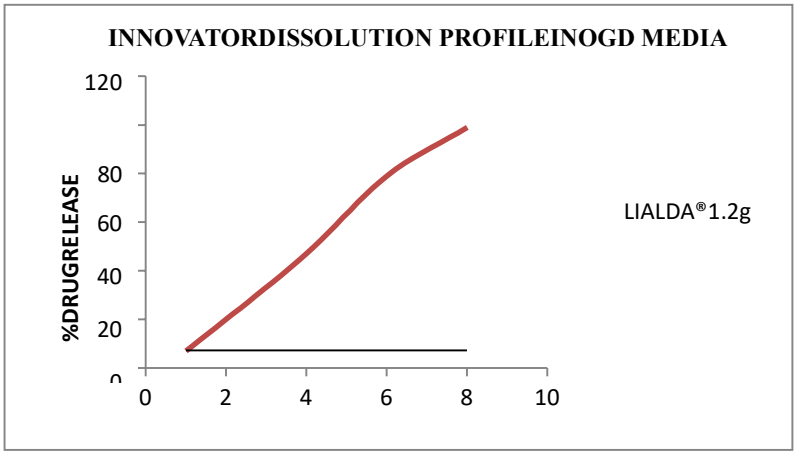
Temperature	37.0±0.5^{0}C	
Apparatus	USPtype II	
PaddleRPM	100RPM	
DRUGRELEASEMEDIA	**VOLUME**	**SAMPLINGTIME POINTS**
Acidstage0.1 N HCLfollowed by	750 ml	2hrs.
BufferstageI:P^{H}6.4phosphatebuffer followed by	950 ml	1 hr.
BufferstageII:P^{H}7.2phosphatebuffer	960 ml	1,2,4,6,8 hrs. and infinity
Detection wavelength	330nm	

DISSOLUTION PROFILE OF INNOVATOR (LIALDA 1.2 g) AND TEST DRUG PRODUCTS:

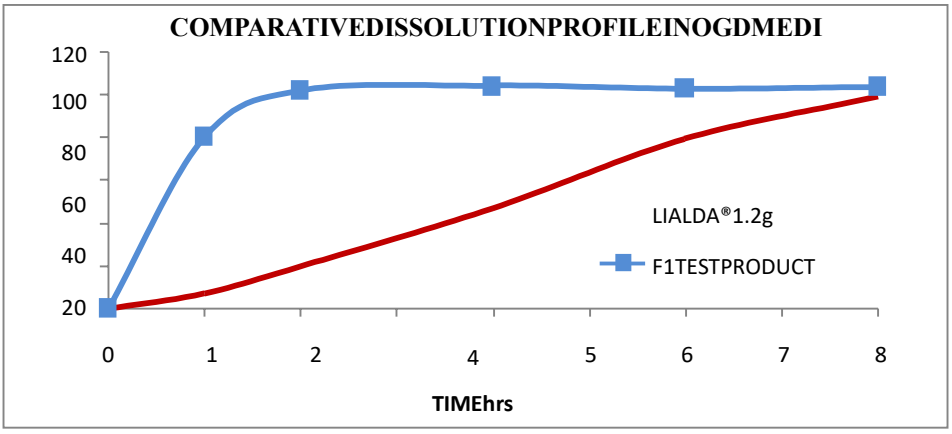
In acid stage the innovator and test drug products does not show any drug release for 2 hrs and in buffer stage I innovator drug product shows little or no drug release and test drug product does not show any drug release for 1 hr. So dissolution studies were carried in drug release media (Buffer stage II) for both innovator and test drug product.

Plot 1: Dissolution profile of innovator drug product in OGD media (PH 7.2 phosphate buffer):

Plot1:Innovatordissolutionprofilein OGDmedia:

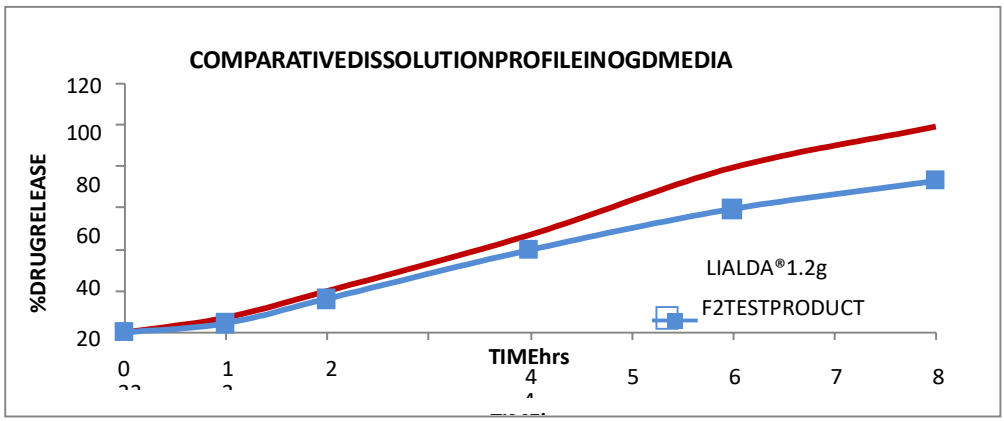


Plot2:Comparativedissolutionprofileofformulation–1(testdrugproduct)in OGD media:



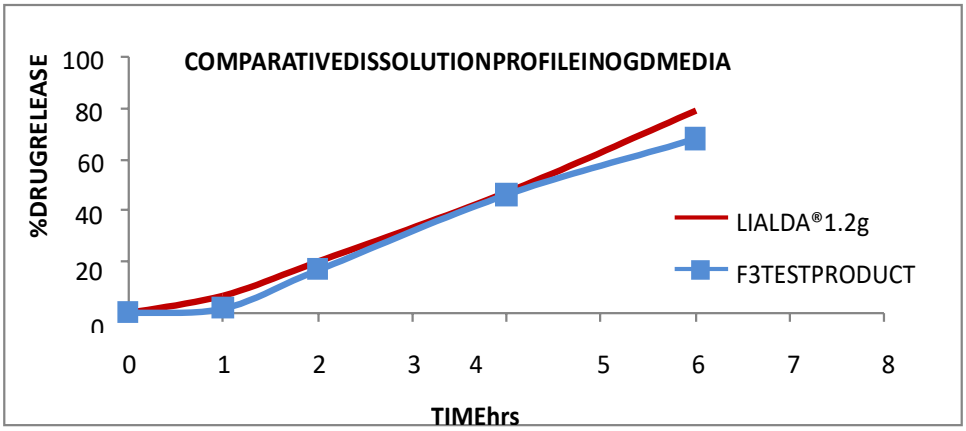
Based on the above dissolution data, the test product shows higher release profile compared to that of innovator product. This might be due to higher % w/w of drug in the dry mix which restricts the use of sufficient quantity of binder in the formulation. So it was recommended to use binders of high viscosity grade instead of low viscosity grade.

Plot3Comparativedissolutionprofileofformulation–2(testdrugproduct)inOGD media:



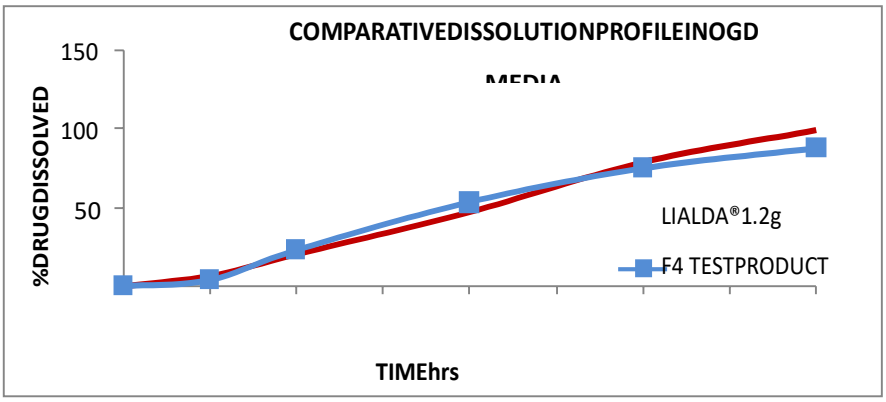
Based on above dissolution data, test product shows comparable and similar release profile during the initial time points (up to 4 hrs) and slower in release in later time points. The drop in dissolution in later time points is due to high viscous grade of binder used. So it can be concluded to use lower % w/w of binder to get desired release profile.

Plot4:Comparativedissolutionprofileofformulation-3(testdrugproduct)inOGD media:



Based on the above dissolution data, the test product shows comparable and similar release profile during the initial time points (till 4 hrs) and slower release in the later time points. There was a significant increase in dissolution at final time point compared to that of Formulation - 2 which was due to decrease in the quantity of release retardant (HPMC K4 M), but still lower when compared to Innovator. Hence, it can be concluded to use lower %w/w of binder to get desired release profile.

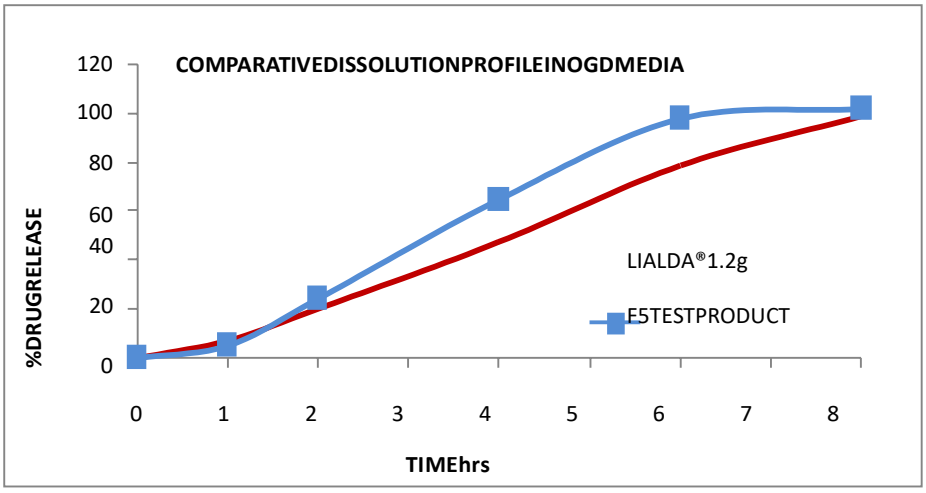
Plot5:Comparativedissolutionprofileofformulation–4(testdrugproduct)inOGD media:



Based on the above dissolution data, the test product shows comparable and similar release profile during the initial time points (till 6 hrs) and slower release in the final time point. There was no complete end release after the final time point due to high binding efficiency of release retardant, HPMC K 4M.

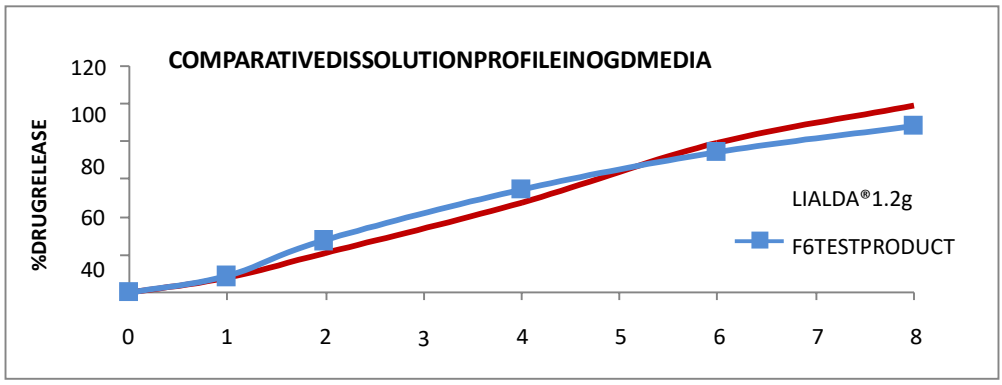
Hence it is recommended to use intra granular disintegrants like Sodium carboxy methylcellulose or Sodium Starch Glycolate to get the complete end release.

Plot6:Comparativedissolutionprofileofformulation–5(testdrugproduct)inOGD media:



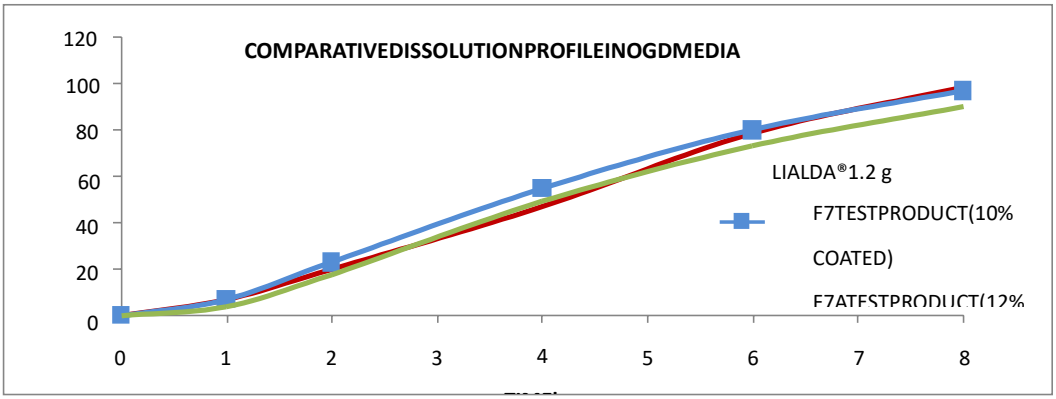
It was observed that the test product shows complete release within 6 hrs indicating the disintegrating effect of Sodium Carboxy methylcellulose added in the intra granular portion. Though the release profile was faster compared to innovator, there was complete end release of drug due to addition of Sodium CMC. So it is concluded to optimize the concentration of Sodium CMC to get the better and desired release profile.

Plot7:Comparativedissolutionprofileofformulation–6(testdrugproduct)inOGD media:



It was observed that the test product shows comparable and similar release profile till 6 hrs., but there was no complete end release, indicating the insufficient amount of Sodium carboxy methylcellulose in the intra granular portion.
So, it is recommended to increase the amount of Sodium CMC with increase in enteric coating build up, to slow down the release during initial hours.

Plot 8: comparativedissolutionprofilesofformulation–7and7A(testdrugproducts)inOGDmedia:

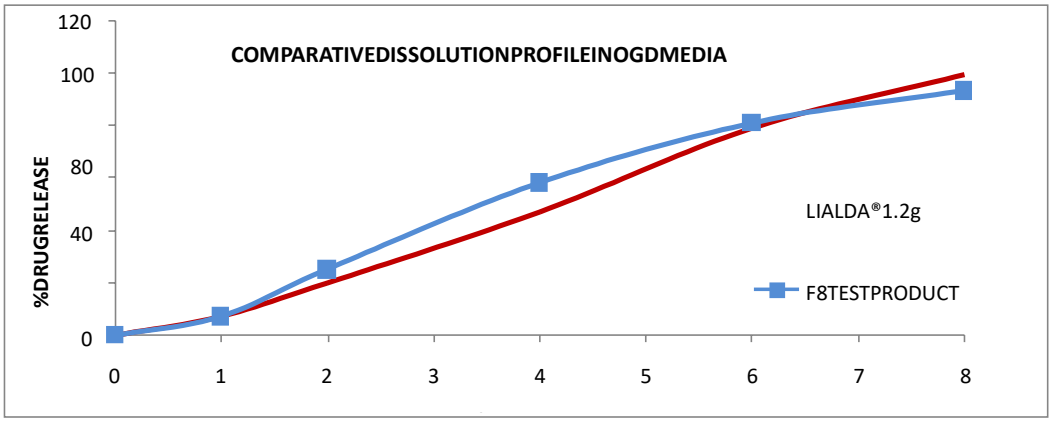


Release profile was found to be comparable and similar to innovator indicating the effect of intra granular Sodium CMC and 10% w/w enteric build up. Release profile with 12% w/w enteric build up was found to be on slower side compared to 10%w/w enteric build up, but the profile was comparable and similar

a. Faster release profile with Sodium CMC at 15mg/tablet and incomplete end release with Sodium CMC at 5mg/tablet.

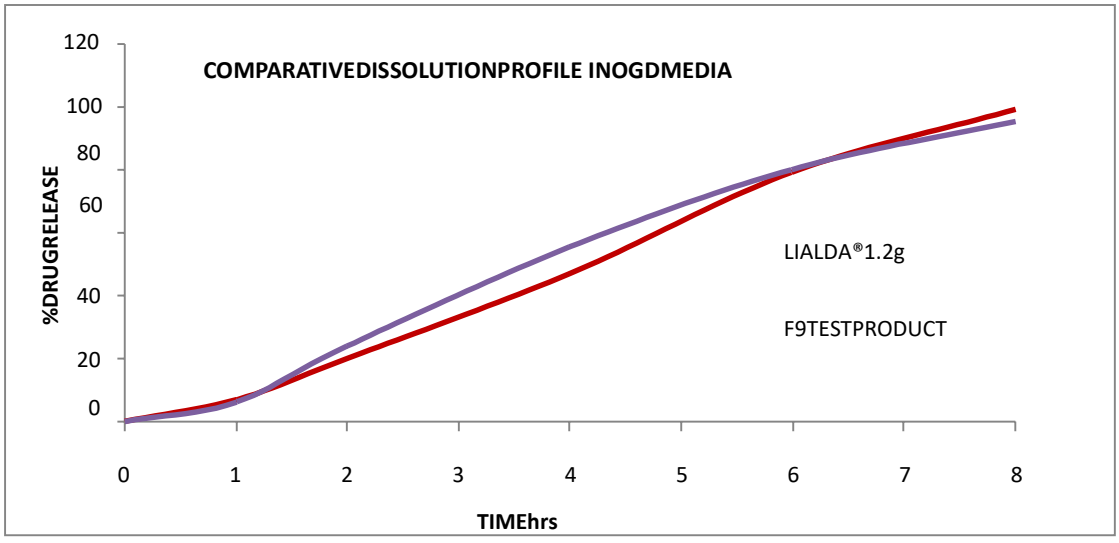
b. Satisfactory results with use of Sodium CMC at 10mg/tablet with increase in enteric coating build up, to slow down the release during initial hours.

Plot9:Comparativedissolutionprofileofformulation–8(testdrugproduct)inOGD media:



Release profile was found to be comparable and similar to innovator indicating insignificant effect of reducing the quantity of binder (Methocel at 9mg/tablet) on dissolution. Physical parameters of dried granules, lubricated blend and core tablets also found to be similar to previous batches with binder quantity at around 18mg/tablet. Hence it was concluded to use Methocel at 9mg/tablet.

Plot 10: Comparative dissolution profile of formulation – 9 (test drug product) inOGD media:



Release profile was found to be comparable and similar to innovator indicating no impact of increased batch size on release profile.

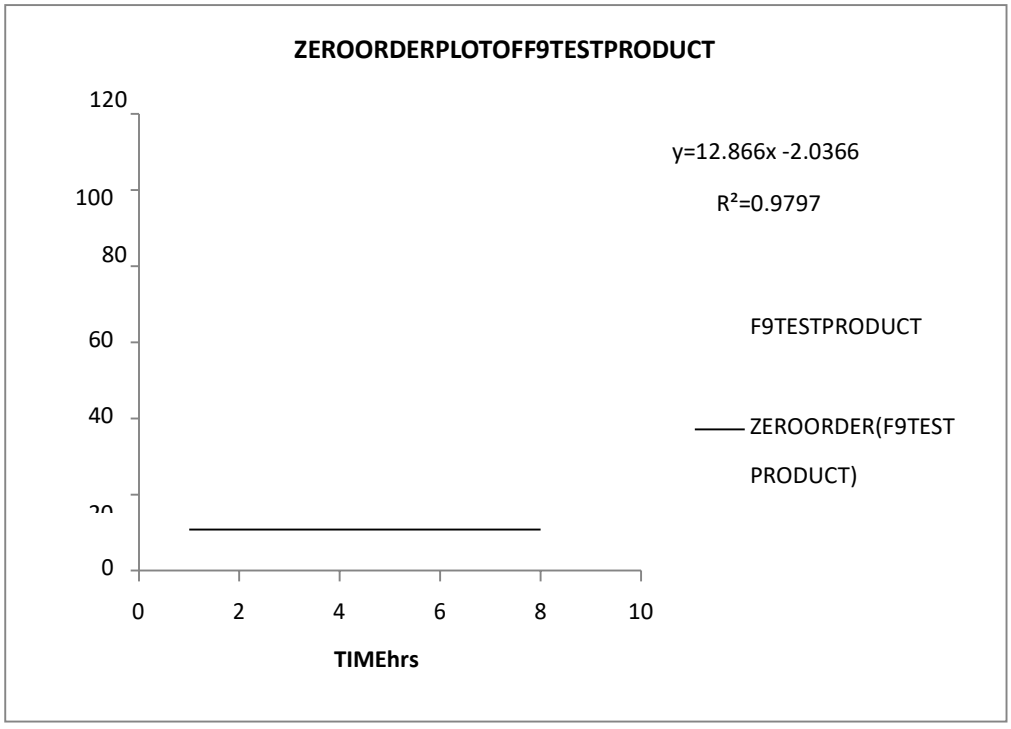
Physical parameters of dried granules, lubricated blend and core tablets also found to be similar to previous batches.

FORMULATION –9:

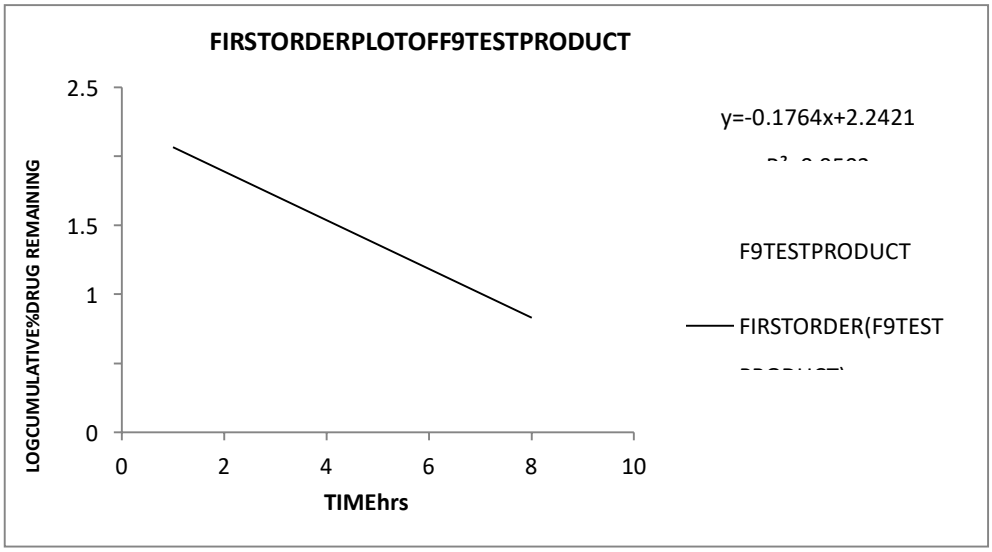
Physical evaluation: Repetition of Formulation - 8 with increased batch size to evaluate the scale up effect on physical parameters and in-vitro dissolution profile.

S. NO.	TEST	RESULTS/VALUES
	Drymix	
1	BulkDensity	0.19gm/ml
	DriedGranules	
2	BulkDensity	0.51gm/ml
	Losson Drying(%)	0.99
	LubricatedBlend	
3	BulkDensity	0.49gm/ml
	Core Tablets	
4	Weight(mg)	1292mg–1328mg
5	Hardness (kP)	18 –21Kp
6	Thickness(mm)	7.30 mm–7.36 mm
7	Friability@100revolutions	0.05 %
	EntericCoatedTablets	
8	Weight(mg)	1440–1450 mg
9	Thickness(mm)	7.61 – 7.75mm

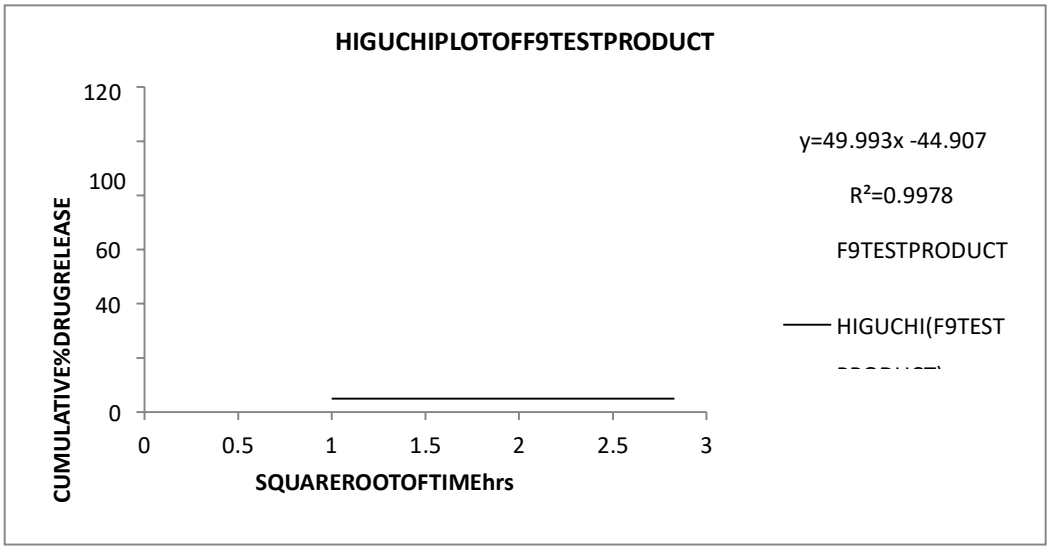
DRUG RELEASE KINETIC MODELS OF FORMULATION – 9 TEST DRUG PRODUCT:



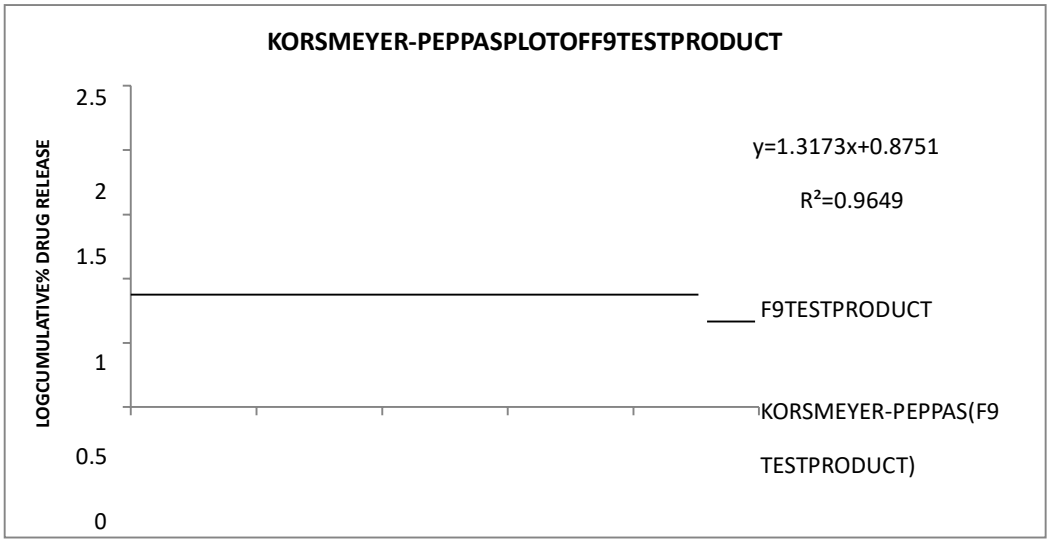
PLOT20: FIRSTORDERMODEL:



PLOT21:HIGUCHIMODEL:



PLOT22:KORSMEYER–PEPPASMODEL:



Comparison of drug release kinetics:

PRODUCT	MODELS OF DRUG RELEASE KINETICS				
	ZERO ORDER	FIRST ORDER	HIGUCHI	KORSMEYER – PEPPAS	
	R^2 VALUE	R^2 VALUE	R^2 VALUE	R^2 VALUE	'n' VALUE
INNOVATOR	0.995	0.822	0.984	0.994	1.284(SUPER CASE II TRANSPORT)
F8 TEST PRODUCT	0.966	0.981	0.994	0.965	1.245(SUPER CASE II TRANSPORT)
F9 TEST PRODUCT	0.979	0.95	0.997	0.964	1.317 (SUPER CASE II TRANSPORT)

Based on the above information the innovator drug product follows zero order kinetics.

Formulation – 8 test products complies with Higuchi model. Formulation – 9 test products complies with Higuchi model.Formulations contain hydrophilic swellable polymers like HPMC as an intra granular ingredient, were described under diffusion-controlled matrix type of controlled drug delivery systems and these systems were explained by Higuchi.

In the present study, formulations contain swellable polymers such as Methocel (Low viscous grade) and HPMC (High viscous grade) , so test drug products of optimized formulation – 8 and formulation – 9 are considered to be matrix formulations and the matrix tablets are complies with Higuchi model, conformed by drug release kinetics study.STABILITY STUDIES: According to ICH Q1 A (R2) guide lines (stability testing of new drug substances and new drug products) accelerated and long-term stability studies were performed on the optimized and finalized formulation – 9 (F9) test drug product and it was kept under accelerated stability studies for a period of 3 months and long-term stability studies for a period of 3 months.

The coated tablets of formulation – 9 were loaded into a clean100 CC H.D.P.E container with 38 mm child resistant closure without desiccant and induction sealed using induction cap sealer and labelled according to the conditions to be kept. Based on the above information produced after accelerated and long-term stability studies all the parameters of the formulation – 9 test drug products were complies with specified limits. The tablets were physically stable without observable changes.

4) Conclusion

Among all the formulations optimized formulation – 9 (F9) test drug product contained 9.0 mg/unit of Methocel (Low viscous grade) as a binder, 50 mg/unit of HPMC (High viscous grade) as a release retardant and 10.06 % w/w of enteric coating build up at an enteric polymers ratio (Eudragit S 100: Eudragit L 100) 1: 2.9 with plasticizers quantity 16.56 % of polymers weight at a ratio (PEG 6000: Triethyl Citrate) of 1: 4.3 showed physical parameters and drug release profile similar to innovator drug product and the similarity factor was found to be 69.

From the 3 months data of accelerated and long-term stability studies, all the parameters of the formulation – 9 test drug products were complies with specified limits. The tablets were physically stable without observable changes. So, it was concluded that the formulated test drug product was quite stable under accelerated and long-term stability conditions.

From the data of drug release kinetics, it was concluded that the innovator drug product follows zero order kinetics and formulation – 9 (F9) test drug product follows Higuchi model.

So, Formulation – 9 was concluded as final formulation.

5. ACKNOWLEDGEMENT :

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