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Formulation and Evaluation of Delayed Release Capsule of Dimethyl Fumarate with Novel Technology

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ABSTRACT
Dimethyl fumarate is an anti-inflammatory agent which is indicated for the treatment of multiple sclerosiswith relapsing formsand for psoriasis. The aim of this study was to prepare and evaluate delayed release capsule of Dimethyl fumarate with raft technology to reduce the flushing, a common side effect. The core mini tablets were prepared by direct compression method &enteric coating was done by perforated coating pan. Pre-formulation studies like angle of repose, bulk density, tapped density, Carr's index,Hausner's ratio & angle of repose were carried out. Evaluation of Post compression parameters such as Hardness, thickness, friability, weight variation disintegration and dissolution. The F05 batch shows the highest drug release at 45 min in pH 6.8 phosphate buffer was 97.13 % which are the satisfactorily results. After that encapsulation done which contains enteric coated mini tablets along with raft blend sothe formulation was formed a complex gel like structure in which mini tablets are trapped and dropped one by one with specified time interval. The F05 was the optimized batch among all six batches & blend 01 among all five blends are selected as per result. The raft technology was successfully applied on delayed release capsule increaseslag time thus decreasing flushing. Stability studies indicated that the developed dosage form was stable and retained their pharmaceutical properties at room temperature and accelerated conditions.

Keywords: Dimethyl fumarate, Raft technology, Delayed release capsules, Relapsing Remitting multiple sclerosis.

INTRODUCTION

A drug can be administered through various route to produce therapeutic effect. Among various routes of administration of drug, oral route is widely accepted by patient. Tablets are the most common used solid dosage form and there is always scope for improving the limitation of tablets like, difficulty in swallowing and delay in the onset of action(Lachman et al 1991). Tablets have many advantages over other dosage forms, such as the low cost of treatment and ease of administration and cause to higher levels of patient compliance and ease of transportation, application and production, high patient compliance, accurate dosing, control of drug release and stability (Carla Lopes M et al 2006). Mini tablets are novel multiple unit solid dosage form which are smaller than 3.0mm or equal in the size 3.0mm in diameter which are usually prepared by multiple tooling (LennartzP, et al1998). Production of mini tablet similar to the production of conventional tablet but in case of mini tablets have high risk of tool damage so they required excellent flow properties of powder because of dies which have small in size, require more controlled in process parameter. One of the main purpose behinds production of mini tablets is patient compliance, for pediatric and elderly patient because they offer less risk of dose dumping, easy swallowing and flexible dosing and they are also more successfully dosage form as multiple unit dosage form (Granules, pellets and mini-tablets) than Single unit dosage forms (Tablets and capsules).These mini-tablets can be filled into hard gelatin capsules or can be compressed as normal tablets. Mini-tablets also offer an alternative for pellets because of their relative ease of manufacturing and because dosage forms of equal dimensions and weight with smooth regular surface are produced in a reproducible and continuous way(Ezgillhanet al 2017).

Dimethyl fumarate is approved for the treatment of relapsing forms of multiple sclerosis. Multiple

sclerosis (MS) is a chronic, inflammatory disease of the central nervous system (CNS) that disrupts the communication between the brain, spinal cord, and other areas of the body(Mayo clinic, 2014). The symptoms of MS can vary widely, depending on which nerves are affected and on the extent of the nerve damage.The most common symptoms associated with MS include fatigue, numbness, spasticity, vision problems, and bowel and bladder problems.

Gastro-retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Over the last few decades, several gastro-retentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bio-adhesion to stomach mucosa un-foldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, super porous hydrogel systems, magnetic systems, Raft system etc. (Amit Kumar et al 2010). A simple meaning of Raft is a flat structure, typically made of planks, logs, or barrels, that floats on water and is used for transport or as a platform for swimmers (Bhavsar D.N et al 2011).

MATERIALS AND METHODS

Materials

Dimethyl fumarate was obtained as Gift sample from Sun Pharma Research centre Gurugram, Microcrystalline cellulose (JRS Pharma), Croscarmellose Sodium (FMC International), Colloidal silicon dioxide (Evonik) Magnesium Stearate (Peter Greven)Eudragit L100 (Evonik), Triethyl citrate, Isopropyl alcohol, Eudragit L 30 D-55 (Evonik), Talc were of analytical grade, Simethicone, Sodium alginate (FMC International), Pregelatinized starch (Nacron fine chemicals), Sodium bicarbonate (MFR-fishers scientific), Calcium carbonate (MFR-fishers scientific).

Methods

Identification of absorption maxima (λmax)

The Model drug dimethyl fumaratewas mixed with pH6.8 phosphate buffer to a concentration of 10µg/ml. The prepared solution was scanned between 200-400 nm region on UV Spectrophotometer (shimadzu 1700 CE) in order to identify the absorption Maxima (λmax).(USP 2018)

Fourier Transform Infrared (FTIR) spectral analysis

The model drug, Dimethyl fumarate and mixture of drug with different excipients used under this experimental condition were evaluated for compatibility. The evaluation was performed by taking 2 mg sample in 200 mg KBr (Perkin Elmer, spectrum-100, Japan).The range of scanning was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}(Mohdabdulhadi et al 2014).

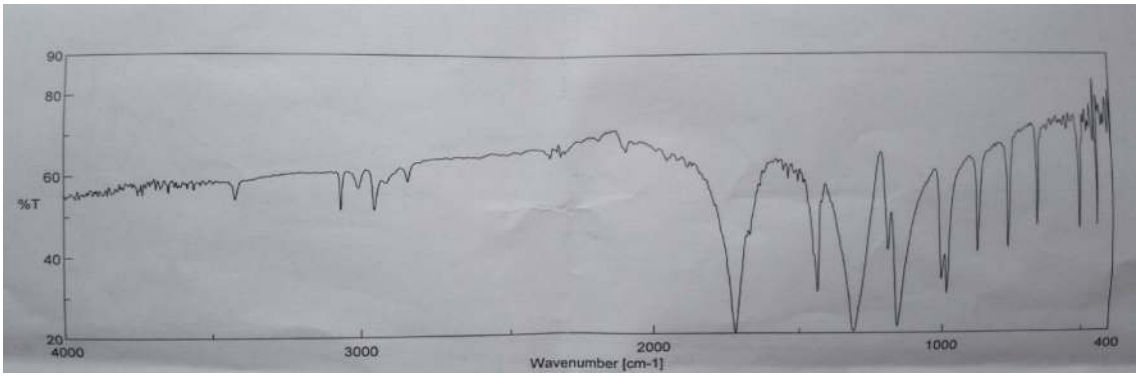


Fig.1 FTIR Spectra of Dimethyl Fumarate

Preparation of core mini-tablets of Dimethyl fumarate

The core mini tablets were prepared using the direct compression method. The ingredients such as Dimethyl fumarate, Microcrystalline cellulose, Croscarmellose Sodium, Colloidal silicon dioxide and magnesium stearate as mentioned in Table 1. Dimethyl fumarate, Microcrystalline cellulose,

Croscarmellose Sodium, were passed separately through sieve # 45.All the materials were taken in poly bag & mix for 15 mins for uniform mixing.The Colloidal silicon dioxide and magnesium stearate were passed through the sieve # 60 and mixed together with the powder mixture in a poly bag for 5 mins to get a uniform blend.The powder mixture was compressed into 20 mg minitablets using 2.5 mm round shaped concavepunches and dies, by using 16 station tablet compression machine. (Cadmach, Ahmedabad, India)(Mohdabdulhadi et al 2014).

Table 1: Formulation of Preliminary Trials F01 to F06

Ingredients	**Amounts(mg/capsules)**					
	F01	**F02**	**F03**	**F04**	**F05**	**F06**
Stage 1:Core mini-tablets						
Dimethyl fumarate (USP)	240	240	240	240	240	240
Microcrystalline cellulose	49.6	47.6	42.6	38.2	35.2	27.6
Croscarmellose Sodium	8	10	15	19.4	22.4	30
Colloidal silicon dioxide	16	16	16	16	16	16
Magnesium Stearate	6.4	6.4	6.4	6.4	6.4	6.4
Core tablets weight	320	320	320	320	320	320

Preparation of enteric coating solution:

Method: Enteric coating solution was prepared by simple solution method.

Seal coating (3%): It was prepared by 3% w/w of Eudragit L100 as an enteric polymer, PEG as plasticizer and isopropyl alcohol was used as solvent. This mixture was constantly stirred for 1h with paddle mechanical stirrer at the rate of 1000 rpm and the stirred coating solution was again filtered through muslin cloth, a seal coating solution was obtained.

Enteric coating (7%): It was prepared by 7% W/W of Eudragit L-30D55 as an enteric polymer, PEG as plasticizer and water &isopropyl alcohol(25:75) mixture was used as solvent as well assimethicone were also used. This mixture was constantly stirred for 1h with paddle mechanical stirrer at the rate of 1000 rpm and the stirred coating solution was again filtered through muslin cloth, enteric coating solution was obtained. After coating used talc as lubrication.

The core minitablets previously warmed to 40 °C, were coated in a perforated coating inlet temperature of 40 °C and a spray rate was 2.5 $ml.min^{-1}$After 10 min, the spray rate was increased to 4.0 $ml.min^{-1.}$ The coating solution (EudragitL100, 3% and EudragitL-30D55, 7% w/v) was applied until minitablets 10% weight gain was achieved. The coated tablets were evaluated for its weight variation, thickness, hardness, Friability and in vitro dissolution study.

Raft technology

Table 3: Composition of raft blend

Ingredient	Quantity/ batch (%)	Quantity/ batch (%)	Quantity/ batch (%)	Quantity/ batch (%)	Quantity/ batch (%)
	Blend 1	Blend 2	Blend 3	Blend 4	Blend 5
Sodium alginate	40	48.0	44.0	25.0	58.0
Pregelatinized starch	25.0	-	58	58	-
Sodium bicarbonate	22.0	24.0	-	17.0	-
Calcium carbonate	13.0	28.0	24.0	-	42.0

The raft blend was prepared by accurately weighed all the ingredients shown in table 3 was passed through the sieve # 40 one by one. All the materials were taken in poly bag & mix for 15 mins for uniform mixing.

Preparation of capsule with enteric coated mini tablets and raft blend

For preparing the capsule formulation fill the blend along with16 minitablets which equivalent to 240 mg of Dimethyl fumarate into the HPMC capsules size 2.After all these steps were followed, delayed release capsules were prepared. The delayed release capsules were evaluated for raft technology by weight variation and in vitro dissolution study.

EVALUATION

Precompression tests

A) Bulk Density: An accurately weighed quantity of powder which was transferred into graduated glass cylinder. After pouring the powder into graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduated marks on the cylinder as ml. the volume measured was the bulk volume and the density were calculated by following formula.

Bulk density= weight of powder/ bulk volume

B) Tapped Density: After measuring the bulk volume the same measuring cylinder was kept into tapped density tester. The tap density apparatus was set to for 500 taps. The tapped density was calculated by the following formula

Tapped Density= weight of powder/tapped volume

C) Carr's index/ Compressibility index: Compressibility index indicate the flow properties of the blend. Low percentage of carr's index indicate free flowing powder, whereas high carr'sindex represent poor flowing powder. Compressibility Index of granules was calculated from the following formula.

Carr'sindex(%) = Dt-Db/Dt*100

Where, Dt is Tapped Density and Db is bulk density

D)Hausner's ratio: Hausner found that the ratio of tapped density to bulk density was related to interparticle friction and could be used to predict powder flow properties. Low Hausner's ratio means that the drug has high flowability. It was calculated using equation given below.

Hausner's Ratio= Tapped density/ Bulk density

E) Angle of repose: The angle of repose was determined by accurately weighed granules as the tip of the funnel touched the apex of the blend. thenthe blend was allowed to flow through the funnel freely on to the surface. From the powder cone, height and radius was measured and the angle of repose was calculated by following equation.

$$\tan\Theta = h/r$$

where, h and r are the height and radius of powder cone respectively.

Post compression evaluation

1. **Appearance:** In this test, randomly selected 20 tablets from each formulation to check physical appearancelike any discoloration or surface roughnessof the mini tablets.

2. **Weight Variation:**Randomly selected 20 tablets of all batches during compression and weight of individual tablets was checked with the help of electronic balance, milligram was the unit which was used to expressed the weight of each mini tablets(Lachman L et al 1991).

3. **Thickness:** The thickness of the tablet is mostly related to the tablet hardness and can be used as initial control parameter. Ten tablets were randomly selected from each formulation and their thicknesses were measured by using Vernier calipers. Thickness values were reported in millimeters(A. Mounika et al 2015).

4. **Hardness:** Randomly selected 10 mini tablets from each batches of mini tablets. The crushing strength of the tablet was measured using Schleuniger type hardness tester by placing the tablet between the anvils and measuring the force required to break the tablet.it was expressed in $kgcm^{-2}$. The Mean value were calculated from each formulation. (A. Mounika et al 2015).

5. **Friability:**Thefriabilator (Electrolab) was apparatus which used to measured friability by placing tablets inside the test apparatus. Friability procedure for tablets which weight has equal to or less than 650 mg, take a

sample of whole tablets corresponding to 6.5 g. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets and loose powder attached on the mini tablets as before and accurately weigh. The friability was calculated as the percentage weight loss(Ezgillhan et al 2017).

$$\% \text{ Friability} = \frac{\text{Wt. of tablets before rotation - wt. of tablets after rotation}}{\text{Wt. of tablets before rotation}} \times 100$$

6. Disintegration: Disintegration test apparatus as per I.P specifications were used to determined*in vitro* disintegration of the enteric coated mini tablets. Place six mini tablets tablet in each of the tubes which present in the basket. Place the disc to each tube present in the basket and start the apparatus using 900ml of dissolution medium as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in dissolution medium maintained at 37°C. The time was observed in sec for complete breakdown of the mini-tablet with no mass was remained in the sieve of apparatus was measured and recorded(Ezgillhan et al 2017).

7.In-Vitro drug release: Dissolution test: Procedure: In vitro release of the drug was determined by estimating the dissolution profile.Drug release studies were carried out using a USP type -II dissolution rate test apparatus (Apparatus 2 ,100 rpm, 37±5º C) for 2 hours in 0.1 N HCl (500ml) as the average gastric emptying time is about 2 hours. Then was replaced with pH – 6.8 phosphate buffer (500ml) and tested for drug release up to complete drug release. At the end of the time period 7 ml of the sample were taken and the dissolution medium analysed for drug content. A 7 ml Volume of fresh and filtered dissolution medium was added to make the Volume after each sample withdrawal and to maintain the equilibrium. Collected Sample was analysed using UV spectrophotometer at 212nm.Drug release from the formulations were evaluated. Linear relations were obtained in the concentration interval 10-50 μgmL^{-1} with correlation coefficients (r) of 0.9965 (pH 1.2), 0.9965 (pH 4.5) and 0.9952 (pH 6.8)(usfda dissolution).

8. Stability studies: Stability studies were performed as per theICH guidelines. Selected formulations of Dimethyl fumarate were packed in container and stored at (40 ± 2 °C / 75 ± 5 % R.H) for a period of 3months. Samples of the selected formulation which are kept for stability condition were withdrawn at definite time intervals. The withdrawn samples were evaluated for physical appearance, weight variation & in vitro release study (Sanjay bajaj et al 2012).

9.Statistical analysis: The data were expressed as mean ± standard deviation and the experimental tests were performed in triplicate. Experimental wise error rate (α) of 0.05 which was used to determine level of significance among all possible pairs of formulations. The level of statistical significance was set at $p \leq 0.05$.

RESULTS AND DISCUSSION

Absorption maxima (λmax)

When model drug Dimethyl fumarate was scanned in between 200-400 nm region spectrophotometrically, absorption maxima was 212nm at buffer pH 6.8 phosphate buffer. Thus, the value of absorption maxima was used in plotting the release profile of Dimethyl fumarate.

FTIR spectra

FTIR spectra analysis showed no chemical interaction between pure drug and excipients as all the peaks remained intact at their position.

Pre- compression parameter

The prepared Dimethyl fumarate powder blend for tabletting was prepared by direct compression method. The prepared Dimethyl fumarate powder blend were evaluated bulk density, tapped density compressibility index, Hausner's ratio and angle of repose as given on Table 4.

prepared pantoprazole powder blend were evaluated angle of repose, bulk density, tapped density, Hausner's ratio

Table 4: Pre- compression parameter

Powder Blend	Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Carr's Index(%)	Hausner's Ratio	Angle of repose (°)

F01	0.42	0.5	17.4	1.21	30.34
F02	0.41	0.49	15.2	1.18	28.88
F03	0.48	0.54	11.11	1.12	29.58
F04	0.47	0.53	11.32	1.12	25.41
F05	0.49	0.56	12.50	1.14	26.64
F06	0.37	0.51	26.58	1.36	40.25

Powder blend for mini-tablets were showed carr's index less than 15.5 %, Hausner's ratio less than 1.18 and angle of repose in the range of 25°41′ to 40°25′. Results indicates that good flow properties of the powder blend were found of trial batches F02, F03, F04, F05.

Post compression parameter

The Dimethyl fumarate core mini-tablets were prepared by direct compression method and were evaluated for their hardness, thickness, weight variation and friability in Table 5.

Table 5: Post compression parameter

Trial Batches	Hardness (5 Tablets) (kg/cm^2)	Thickness (10 Tablets) (mm)	Friability (6.5gm Tablets) (%)	Avg. Wt. (20Tablets) (mg)
F01	3.1±0.23	2.14±0.059	0.71±0.06	20.27
F02	3.5±0.29	2.32±0.029	0.59±0.04	20.73
F03	3.6±0.53	2.34±0.051	0.28±0.06	20.79
F04	3.7±0.23	2.18±0.039	0.10±0.04	20.64
F05	3.8±0.55	2.40±0.012	0.15±0.03	21.16
F06	3.9±0.31	2.35±0.085	0.09±0.07	21.47

Dimethyl fumarateun coated mini-tablet showed the hardness in the range of 3.1 ±0.23-3.9±0.31, thickness in the range of 2.14±0.059 to 2.40±0.012, friability in the range of 0.09±0.07 to 0.71±0.06, average weight in the range of 20.27 to 21.47.

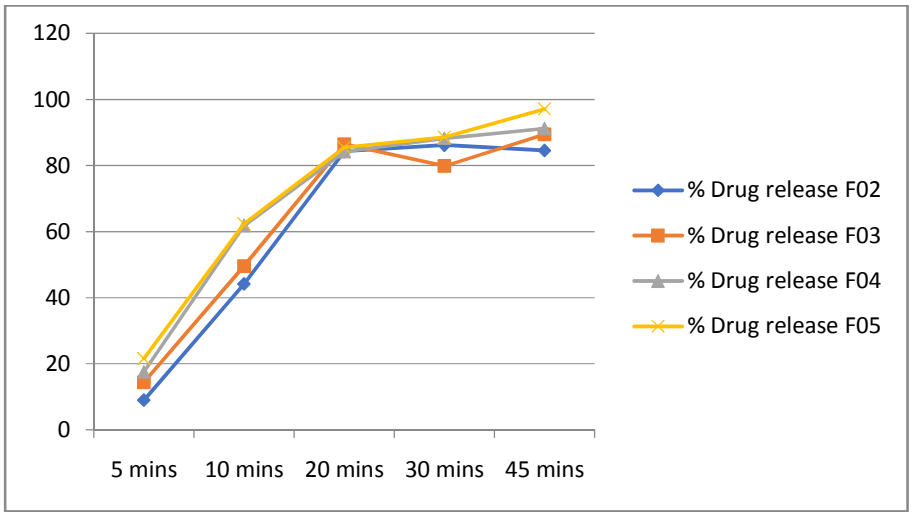
Physicochemical evaluation ofDimethyl fumarate enteric coated mini-tablets:

The tablets which show most satisfactory result in vitro dissolution. The observation of physicochemical evaluation of prepared coated mini-tablets are shown in Table 6. The weight variation was found to be between 0.211 ± 0.024 % to 214 ± 0.021 mg, disintegration within the 15 minutes and dissolution of selected formulation F02 to F05 in the range of 87.5% to 97.13% were observed.

Table 6: In- vitro Release study

Time	pH	% Drug release F02	% Drug release F03	% Drug release F04	% Drug release F05
2 hrs	1.2	0.39	0.225836	0.197606	0.141147
5 mins	6.8	8.92	14.35574	17.507	21.53361
10 mins	6.8	44.11	49.54482	61.79972	62.32493
20 mins	6.8	84.20868	86.48459	84.20868	85.43417
30 mins	6.8	86.13445	79.83193	88.23529	88.58543
45 mins	6.8	84.53501	89.46078	91.21148	97.13011

Fig 2: In- vitro Release study



The release was found to be very less in the 0.1N HCl of F05 formulation and maximum absorption in 6.8 phosphate buffer which is match with theoretical release. However, F05 formulation was taken for further study.

Raft technology evaluation

Raft technology evaluation observed with F05 formulation which contains 16 minitablets along with raft blend in each delayed release capsule by physical observation of dropped mini tablets in the media.Blend1 with 150mg of blend quantity shown the better result. All the minitablets were

dropped in 0.1 N dissolution media within 45 mins.

Evaluation Test for Encapsulated Mini-tablets

The Evaluation of F05 formulation after encapsulation which contains 16 enteric coated mini-tablets and 150 mg of raft blend. The weight variation was found to be between 0.211 ± 0.024 % to 214 ± 0.021 mg, disintegration within the 15 minutes and dissolution of selected formulation F02 to F05 in the range of 87.5% to 97.13% were observed.

The F05 formulation had a drug release at the end of the acid release period of approximately 0.14%, and in pH 6.8 Phosphate Buffer drug release approximately 97.13% after 45 minutes hence this result was matched with theoretical release so we selectedF05 formulation for further study. Raft technology applied as blend was prepared and filled in the capsule with mini tablets.Evaluation done by observation that during 45 min all minitablets were dropped in the medium.

Table 7: Observation table Number of minitablets dropped in the media.

Dissolution condition: 500 ml, 100 rpm, USP II									
Media	0.1 N HCl	pH 4.5 acetate buffer	pH 6.8 acetate buffer	0.1 N HCl					
Blend	Blend 1						Blend 2	Blend 3	Blend 4	Blend 5
Blend quantity	250 (After tapping)			100	150	200	150.0			
5 mins	2-5	3-5	10+	2-5	5-7	3-6	2-12	No raft formulation		Lump formation observed
10 mins	3-6	7-12	12+	3-10+	6-10	4-8	5-14+			
15 mins	3-8	12+	12+	4-10+	9-12	4-9	6-15+			
20 mins	5-9	12+	12+	5-12+	10-12+	5-10	7-15+			
25 mins	8-10	12+	12+	6-12+	11-12+	6-10	8-15+			
30 mins	8-10	12+	12+	7-12+	12-15+	7-12+	9-15			

45 mins	9-10	12+	12+	8-15+	12-15+	8-12+	10-15+		

DISCUSSION

FTIR studies confirm that there was no chemical interaction between drugs and excipients as all the peaks were intact from other peak. The pre-compression data of F05 formulation indicate good flow properties of the blend,post-compression data were within limits and also indicate that the core mini tablets possess sufficient mechanical strength to resist breakage during coating.

In the present study in which research work was carried out, the aim of this study, Dimethyl fumarate which was used to treatment of relapsing Remitting multiple sclerosis show some side effect in early stage, by keeping this fact in mind to formulatea delayed release capsule with novel technology

The objective in dissolution testing in different media such as 0.1 HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer were added in different composition which increase the lag time minitablets trapped in raft blend dropped take some time after gastric emptying stomach some minitablets reach to basic medium and release the drug slowly which reduce the flushing problem.

The stability studies of F05 formulation were performed by check *in vitro* release profile. The observation which was conclude that there was small variation, thus it was confirmed that F05

formulation was stable for a period of 3 months as per ICH guidelines.

CONCLUSION

This study proposed the development of delayed release capsule gastro-resistant drug- dimethyl fumarate containing 16 enteric coated minitablets and 150mg raft blend. The minitablets contained different concentration of disintegrant and were coated with Eudragit® 100 (seal coat 3%),Eudragit® L30D55(enteric coat 7%). Raft composition contain Sodium alginate, Pregelatinized starch, Sodium bicarbonate, Calcium carbonate which form good complex and trapped the minitablets for 45 minutes in 0.1 N HCl which reduce the flushing due to lag time increase.However, the formulation F05 show the dissolution profile was 97.13%. A stable delayed release capsule of Dimethyl fumarate with raft technology was successfully developed.

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