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Development And Evaluation of Delayed-Release Tablets of Mycophenolate Sodium

R.Margret Chandira[*1], Binod Kumar[2], K. P. Sampath Kumar[3], Digpati Roy[4], Debjit Bhowmik

1. Department of Pharmaceutical Sciences, Vinayaka Missions College of Pharmacy, Salem, India [Email: debjit_cr@yahoo.com]
2. Coimbatore Medical College, Coimbatore, India
3. KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, India
4. Karpagam University, Coimbatore, Tamilnadu, India

Delayed-Release Drug Delivery Systems has a delayed absorption from the gastrointestinal (GI) tract in comparison with Convential Drug Delivery Systems, thereby potentially reducing GI adverse events. The goals of therapy are to suppress the immune response and decrease the host's inflammatory response. Immunosuppressive therapy is often nonselective; protective as well as destructive immune responses are suppressed. Immunosuppresses patients are predisposed to life-threatening infections. In addition, the immunosuppressive drugs frequently cause serious adverse effects. Prevent rejection and kidney graft loss. From the chromatogram of drug in HPLC it was also concluded that the drug had λmax of 254.0 nm, which was exactly similar as reported. FTIR study confirmed the presence of all prominent peaks indicating its authenticity. The physical parameters of drug as well as excipients concluded that these were considerably good to formulate the tablet using wet granulation method. From the overall observations of different evaluative studies, delayed property, water uptake study and in vitro release study tablet of batch F8 was selected as the optimum batch among all batches and further evaluated for the extended parameters. Dissolution data of the tablet of batch F8 was subjected to the treatment with different kinetic equations, which showed that release patterns are best fitted to the first order release equation and involves combination of polymer relaxation and consequently swelling.

Keyword: Beck Depression Inventory, Self-Report, Depression Rating

1. Introduction

Delayed-Release Drug Delivery Systems has a delayed absorption from the gastrointestinal (GI) tract in comparison with Convential Drug Delivery Systems, thereby potentially reducing GI adverse events. Delay the drug action and effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern, as drug using appropriate polymers and localize drug action by spatial placement in the system adjacent to or in the diseased tissue or organ. The total cost of the delayed release product could be lower than the immediate release products. With reduction in side effects the overall expense in disease management also would be reduced. Results of delayed release properties study reveals that all tablets except tablet of batch F6&F7 had good delayed release properties.

This might be due to the less buildup of enteric coating solution. These finding were supported that 12% buildups require for delayed release. Below this, it may show release in gastric fluid when dosage form comes in contact and produce gastri irritation.

The probable reasons behind the cracking properties of tablet of batch F6&F7 was might be less coating used. Further the tablet of batch F8 was subjected to extended evaluation, like effect of various dissolution apparatus over the drug release and effect of different dissolution apparatus.From the results of the effect of dissolution apparatus study, it was cleared that, Use of type I apparatus for dissolution study to the swell able delivery system appeared to inhibit the three dimensional swelling process of the dosage form and consequently suppressed the drug release from formulation. Dissolution parameter shows satisfactory dissolution profile, but shows maximum dissolution at 60 minutes. From the results of in vitro release study, it was observed that the tablet of batch F8 gave highest % cumulative drug release which might be due to the presence of good disintegrating agent.

2. Material And Methods

Mycophenolate sodium procured from Biocon Ltd,Bangalore, HPMC, Ethyl Cellulose , procured from Colorcon Asia Pvt.Ltd,Talc and Magnesium stearate purchased from Loba chemie,cochin.

2.1 Methods

Manufacturing Methods: Mycophenolate sodium

Sifting

- Sift the following ingredients through #40 and load into RMG.
- Mycophenolate Sodium #40
- Microcrystalline cellulose 101 #40
- Sodium starch glycol ate #40

Dry mix for 5 mins.

Binder Preparation:

Disperse Ethyl cellulose in isopropyl alcohol and finally add Methylene chloride

Granulation:

- To the dry mix parts add binder solution and granulate till granules formed.

Drying:

- Dried in fluid bed dryer till target LOD reach by using Moisture Analyser.

Milling:

- Sift dried granules through #20 and retention milled in 1.5 mm screen multi mill.

Lubrication:

- Sift colloidal silicon dioxide #30, sodium starch glycolate #40, and blend with above dried sifted granules for 10mins in conta blender.
- Sift Magnesium stearate 60#, Talc#60 and load into conta blender and blended for 5 mins.

Compression:

Compressed with 9.oomm standard concave punch

Dissolution Study

Dissolution: dissolution test for enteric coated tablets is performed in two stages

i) Acid stage
ii) Buffer stage

Acid stage:

Place 900 ml of 0.1 N HCl is placed in the dissolution apparatus and assemble the apparatus. Maintain the temperature at 37±0.5^{o}C. Operate the apparatus for 2 hrs at 75 rpm. After 2 hrs with draw an aliquot of the fluid, and proceed immediately as directed under buffer stage. Measure the amount of drug release by measuring the absorbance at 306 nm in a UV/Visible spectrophotometer.

Manufacturing Formula:

Table:1 Composition of Each Batch

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Dry mix								
Mycophenolate Sodium	192.35	192.35	192.35	192.35	192.35	192.35	192.35	192.35
Micro crystalline cellulose (101)	83.15	73.65	60.65	62.65	58.65	58.65	58.65	58.65
Sodium Starch glycolate	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
Binder								
Ethyl cellulose	3.00	6.00	3.00	6.00	6.00	6.00	6.00	6.00
IPA/$Mecl_2$	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Lubrication								
Sodium Starch glycolate	---	---	12.00	12.00	12.00	12.00	12.00	12.00
Colloidal Silicon Dioxide	1.00	3.00	3.00	2.00	6.00	6.00	6.00	6.00
Magnesium Stearate	0.50	3.00	7.00	3.00	3.00	3.00	3.00	3.00
Talc	---	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Total	300	300	300	300	300	300	300	300

Table 2: Composion of Each Batch After Addition of Coating Excipients

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Seal coating (2%)	---	---	---	---	2%	2%	2%	2%
Hydroxy propyl methylcellulose	---	---	---	---	5.00	5.00	5.00	5.00
Tri-ethyl citrate	---	---	---	---	1.00	1.00	1.00	1.00
IPA/$Mecl_2$	---	---	---	---	qs	qs	qs	qs
Total	300.00	300.00	300.00	300.00	306.00	306.00	306.00	306.00
Enteric coating						8%	10%	12%
Poly vinyl acetate pthalate	---	---	---	---	---	10.00	16.00	22.00
Polyethelene glycol6000	---	---	---	---	---	4.00	4.00	4.00
Talc	---	---	---	---	---	2.00	2.00	2.00
Titanium dioxide	---	---	---	---	---	2.00	2.00	2.00
IPA/Mecl2	---	---	---	---	---	qs	qs	qs
Total	300.00	300.00	300.00	300.00	306.00	324.00	330.00	336.00

Table 3: Evaluation Parameter of Tablet Batch $F_1$to F_8

Trial	Wt.Uniformity (mg)	Diameter (mm)	Thickness (mm)	Friablity(%)	Hardness(N)	Disintegration time(min)
F1	300±5%	9.0±0.2	3.4±0.2	0.08	40-50	25-30
F2	300±5%	9.0±0.2	3.4±0.2	0.09	70-100	25-30
F3	300±5%	9.0±0.2	3.4±0.2	0.06	70-100	11-12
F4	300±5%	9.0±0.2	3.4±0.2	0.14	70-100	11-12
F5	306±5%	9.0±0.2	3.5±0.2	---	80-120	12-13.5
F6	324±5%	9.3±0.2	3.6±0.2	---	70-180	16-18
F7	330±5%	9.3±0.2	3.6±0.2	---	70-180	17-18
F8	336±5%	9.3±0.2	3.6±0.2	----	70-180	19-21

Buffer stage:

Darin the acid from vessel and add 900 ml of pH6.8 phospahate buffer and maintain the temperature at 37±0.5°c. Operate the apparatus at 75 rpm for 60 mins. Collect the samples at regular time intervals. Measure the amount of drug release by measuring the absorbance at 254 nm in a HPLC.

Calculation:

$$\textbf{Assay \%} = \frac{AT}{AS} \times \frac{WS}{50} \times \frac{5}{50} \times \frac{50}{WT} \times \frac{50}{5} \times \frac{P}{100} \times 1000 \times AV$$

Where,
AT= average peak area of Mycophenolate sodium in sample preparation.
AS = average peak area of standard preparation.
WS = weight of Mycophenolate sodium working standard taken for standard preparation in gram.
WT = weight of sample taken for sample preparation
P = percent purity of Mycophenolate sodium working standard
AV= average weight of tablets taken in gram.

Table 4: Dissolution data of Mycophenolate Sodium tablets in of 0.1 N HCL

Batch no.	Time(min)	0.1 N HCL Release
F6	60	1.7
F7	60	1.6
F8	60	1.4

Result: The Cumulative drug release in 60 min in 0.1 N HCL maximum as in Table no-17

Table 5: Dissolution data of Mycophenolate Sodium tablets in of 0.1 N HCL

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
10	13.39±1.01	9.65±0.92	6.93±0.79	8.01±1.13	22.06±1.03	26.6±0.86	30.99±1.20	19.00±1.08
20	35.02±0.77	38.68±1.23	34.22±0.81	38.68±1.16	54.81±1.12	59.99±0.79	65.61±0.83	50.10±0.80
30	63.61±0.79	68.8±0.90	60.54±0.93	68.8±0.82	79.34±0.79	81.2±0.68	85.24±0.79	71.00±0.75
45	71.93±0.95	72.02±1.13	65.64±0.86	72.02±0.86	85.24±0.88	88.5±0.54	91.21±0.70	94.50±1.03
60	82.06±0.84	79.55±0.72	80.37±0.76	85.33±0.78	91.21±0.92	101.4±0.62	98.14±0.81	102.9±0.59

Result: The Cumulative drug release in 60 min is maximum as in Table no-18

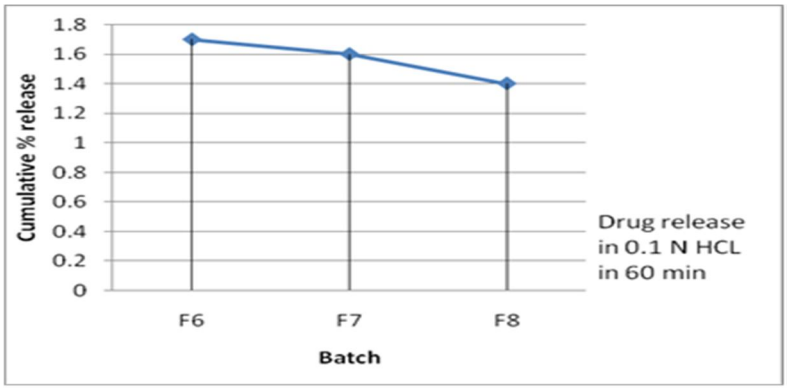


Fig 1: Cumulative % release of F6- F8 in 0.1 N HCL

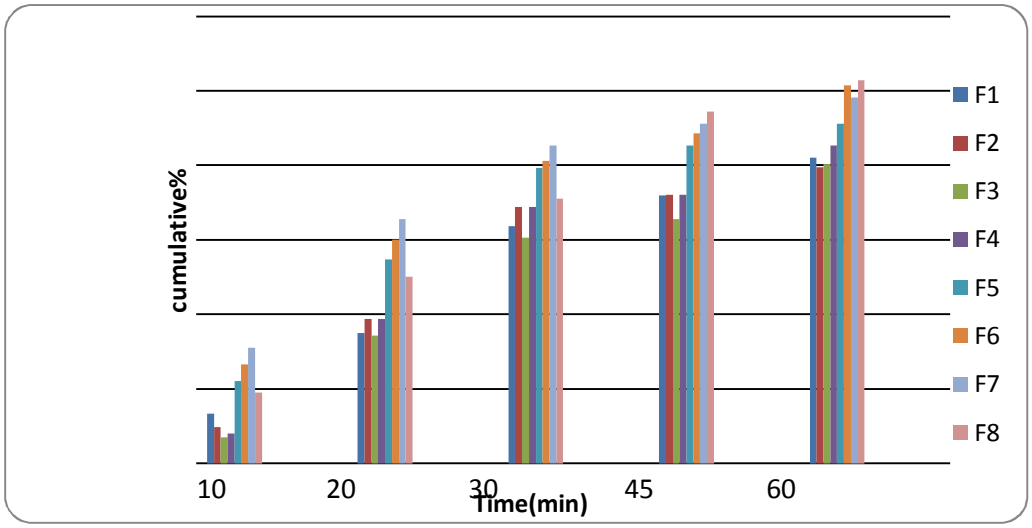


Fig 2: Cumulative % release of F1- F8

Table 6: Dissolution data of tablets of Market sample and to batch F8

Time (min)	Market sample (EUDRAGIT L100) B.No-B/09/1008 BIOCON LTD.	Batch no:F8 (PVAP)
0	0	0
10	5.90±1.2	19.00±1.08
20	41.63±0.o9	50.10±0.08
30	75.93±0.87	71.00±0.75
45	98.81±0.78	94.5±1.03
60	106.30±0.60	102.9±0.59
ASSAY	100.1%	99.3%

*each Value represents the mean ±Standard deviation(n=3)

Result: Dissolution data of tablets of Market sample (B/09/1008 BIOCON LTD.)and to batch F8 as in Table.no-19

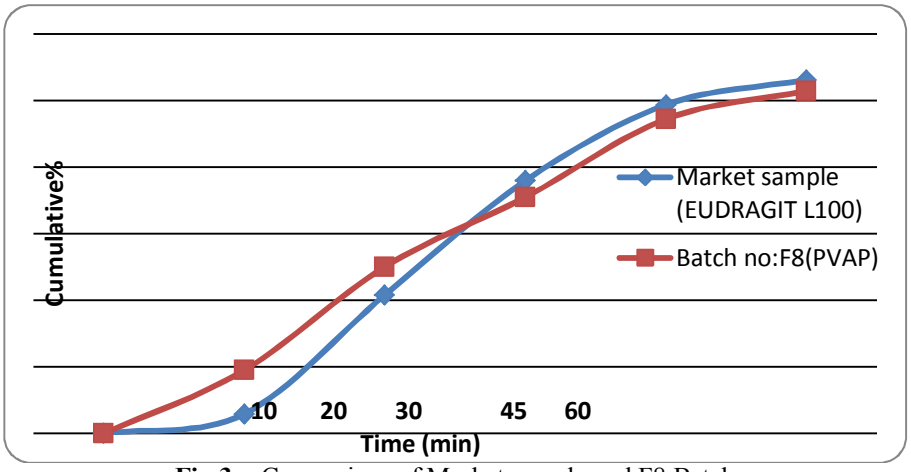


Fig 3: Comparison of Market sample and F8 Batch

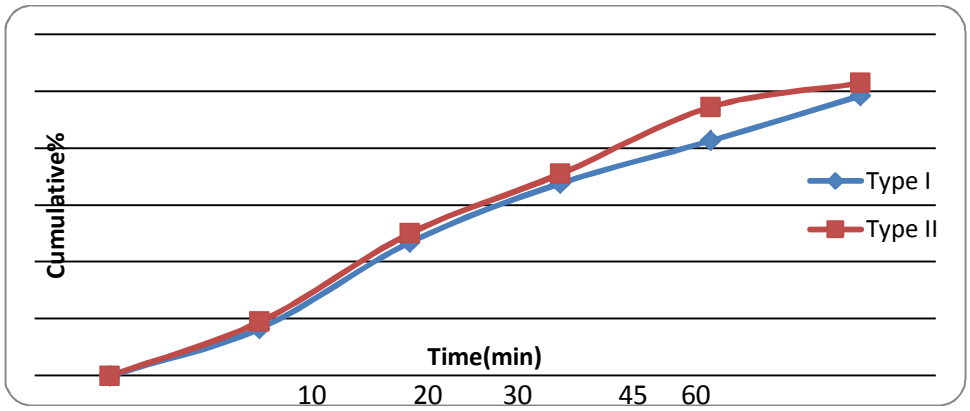
Result: The Cumulative % Drug release profile of pvap was comparatively faster than eudragit L-100(Market Sample) & no need to adjust PH in case of Pvap.as in Fig.no.8

Table 7: Effect of dissolution apparatus on drug release of batch F8

Time (Hrs.)	Dissolution Apparatus (% Release)*	
	Type I	Type II
0	0	0
10	16.67 ±0.76	19.00±0.86
20	46.99 ±0.78	50.1±0.81
30	67.64 ±0.53	71.00±0.51
45	82.65 ±0.59	94.5±0.54
60	98.42 ±0.54	102.9±0.62

*Each value represents the mean ± standard deviation (n = 3)

Fig 4: Effect of dissolution apparatus on drug release of batch F8



Result: The USP Type I apparatus suppresses the three dimensional drug release from the delayed release tablet so the Drug release slower than USP TYPE II.as in Fig.no-9

Stablity Data:

Stability studies performed at, 40°c±2°c/75%±5% RH was performed for all the formulations prepared. Assay and dissolution study were performed for these batches.
Storage condition:40±2°c/75±5%RH
Packaging: Packed in PVC Blister(1×10Nos pack)
Description: White,Circular,biconvex,Enteric coated tablets.

Table 8: Dissolution profile of tablets of batch F8 put on stability study at 40°C/75%RH

Date of Completion	Test interval	Appearence	Average Weight (gm)	Thicknes s (mm)	Hardness (N)	D.T (min.)	Identifica tion	Dissolution (%)
19/11/2009	Initial	Complies	3.36	3.6±0.2	122.2	15´35”	Complies by HPLC	102.9%
20/12/2009	1 Month	Complies	3.35	3.6±0.2	119.6	15´40”	Complies by HPLC	100.6%
20/01/2010	2 Month	Complies	3.33	3.6±0.2	119.2	15´42”	Complies by HPLC	98.3%

Result: From above data it was found that product is stable for 2 month & kept for further study as in Table no-21

3. Conclusion:

From the literature review it is clear that Mycophenolate sodium (delay release) is Result of batch F1 to F8 shows improvement of drug release.. From the in-vitro dissolution study it was concluded that tablet of batch F8 showed highest percentage cumulative drug release due to combination of poly vinyl acetate phthalate., while the tablet of batch F6 & F7rapid drug release (due to less coating) than tablet of batch F8 in Stomach so it may cause irritation . From the overall observation of different evaluation studies tablet of batch F8 was selected as an optimized batch .From the study between

different polymers, poly vinyl acetate phthalate shows better release profile.

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