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Studies On Decisive Components In Osmotically Controlled Release Oral Delivery System Of Pregabalin

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Abstract: Pregabalin is absorbed in the small intestine and proximal colon and poorly absorbed beyond hepatic flexure. In immediate release dosage form most of the drug gets eliminated from the body because of short half life and narrow absorption window. In conventional extended release dosage form beyond 6 hours would be wasted because the dosage form has travelled beyond the hepatic flexure. Osmotic drug delivery system with bigger size of dosage form (not to pass pyloric sphincter) is good choice to address the identified issues.

The present study aimed to design the formulation which retains in the stomach and release the drug. In the development of the formulation of Pregabalin Microcrystalline cellulose, Mannitol, Povidone, Colloidal silicone dioxide and magnesium stearate are used to form the tablets. To get the extended release action of the Pregabalin, Cellulose acetate and PEG are used as extended release coating component. Tablets were prepared by using wet granulation technology; blend and uncoated tablets were evaluated for different inprocess parameters. After extended release coating of the tablet it is further drilled for suitable orifice diameter to achieve the desired drug profile. Based on physical parameters and dissolution results of various trials of the product Formulation F9-330 was selected as optimized formulation. This particular batch has been kept on stability as per the ICH recommendations. Hence the extended drug release can be achieved by using OROS technology

Keywords: Pregabalin, Cellulose actetate, OROS, Mannitol

1. Introduction:

Pregabalin is used in the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. It is used as adjunctive therapy for the treatment of partial-onset seizures in patients 1 month of age and older. Furthermore, it is recommended for management of fibromyalgia and neuropathic pain associated with spinal cord injury.

Currently Pregabalin is available in immediate release as well as extended release form commercially. Pregabalin is absorbed in the small intestine and proximal colon and poorly absorbed beyond hepatic flexure. In immediate release dosage form most of the drug gets eliminated from the body because of short half life and narrow absorption window. In conventional extended release dosage form beyond hours would be wasted because the dosage form has travelled beyond the hepatic flexure in 6hrs. Osmotic drug delivery system with bigger size of dosage form (not to pass pyloric sphincter) is good choice to address the identified issues. A gastroretentive osmotic drug delivery system is useful for delivering the drug in upper part of gastrointestinal

tract (GIT) and it is most efficient in presence of adequate food and fluid. This drug delivery system remains unaffected by gastric emptying rate and peristaltic movements of GIT. Higher dose of drug and high solubility in water rationalize the choice for developing unitary core osmotic pump.
Although Pregabalin is already available in extended release dosage form but is having following disadvantages;

1. Dose dumping of the formulation due to cracking or breaking of the tablets.
2. In matrix formulation there is always variation in the drug release pattern
3. Existing tablet is having length more than 22mm ie 23.0mm which is quite bigger tablet. This bigger size of the tablet may impact the patient compliance due to its size and fear of choking the tablet. So we have proposed the smaller size of the tablet to improve the patient compliance.
4. Existing formulation has used water sensitive polymer which deforms or expands the dimension of the tablet during ageing and handling of the product.
5. Current ER formulation is matrix type of formulation which follows the first order kinetics so release will be depend upon the amount of drug available for release of the drug.

Initial risk assessment of the formulation was performed for osmotic tablets of the Pregabalin. Mannitol, Rate controlling coating (Cellulose Acetate and PEG) identified as critical materials (Decisive component) of the formulation which may impact the drug release of the product. Furthermore, initial risk assessment was performed for drilled tablet, where orifice diameter was identified as critical process parameter (CPP) which may impact the drug release of the product. These formulation variables and critical process parameters proposed to study to understand its decisive role in the osmotic drug delivery system of Pregabalin Extended release tablets 330mg.

2. Materials and Methods:

Materials:

Pregabalin was a gift sample obtained from Hikal., Navi Mumbai, India. Cellulose Acetate CA 398-10, Microcrystalline cellulose & Mannitol samples were purchased from Signet Chemicals, Mumbai, India. Magnesium stearate and Colloidal silicone dioxide purchased from S.Zaveri Chemicals, Mumbai, India. Polyethylene Glycol and Povidone are obatined from BASF, Navi Mumbai, India as gift sample.

Methods:

2.1 Formulation of Osmotically regulated oral systems tablets of Pregabalin (Pregabalin Extended Release Tablets) : Accurately weighed quantity of Pregabalin API and other excipients were sifted through nominal aperture of 420 µm (No. 40 sieve). All these ingredients were loaded in the rapid mixer granulator and mixed for 5mins to form the dry mix. This dry mix is further granulated using aqueous binder to form the proper wet mass granules. These granules dried in the fluidized bed dryer at 50°C and further milled through Co mill by using 1.0mm screen. These granules were sized through 20mesh and loaded in the cone blender along with lubricant. This blend was mixed for 5mins to lead the uniform mixing of all the ingredients together.

Table 1. Comparative Composition of Pregabalin Extended Release Tablets 330mg

Ingredients	F1-330	F2-330	F3-330	F4-330	F5-330	F6-330	F7-330	F8-330	F9-330
Pregabalin	330	330	330	330	330	330	330	330	330

Microcrystalline Cellulose	218.6	216.6	208.6	138.6	126.6	128.6	136.6	206.6	173.1
Mannitol	156.8	156.8	156.8	236.8	236.8	236.8	236.8	156.8	196.8
Povidone	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3
Colloidal Silicone Dioxide	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Magnesium Stearate	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0
Cellulose Acetate	36.2	36.2	46.2	36.2	46.2	46.2	36.2	46.2	41.2
Polyethylene Glycol	3.5	5.5	3.5	3.5	5.5	3.5	5.5	5.5	4.0

***** All weights were expressed in mg.

2.2 Evaluation of powder blends

2.2.1 Bulk density (BD)

Bulk density was determined by pouring the weighed powder blend (previously passed through No.22 sieve) into a calibrated measuring cylinder and the powder surface was leveled with glass rod without applying any pressure. The bulk volume was recorded and the bulk density of powder blend was determined using Eq.(1)[18, 19].

$$\text{Bulk density} = \frac{\text{Bulk weight}}{\text{Bulk volume}} \quad (1)$$

2.2.2 Tapped density (TD)

Tapped volume of known mass of powder blend was determined by tapping the measuring cylinder till a constant blend volume was observed (Electrolab, ETD-1020) . Tapped density was calculated using Eq. (2)[18, 19].

$$\text{Tapped density} = \frac{\text{Powder weight}}{\text{Tapped volume}} \quad (2)$$

2.2.3 Angle of repose (AR)

The funnel was fixed to a stand at a definite height and powder mixture was allowed to flow through it. The angle of repose was determined by measuring the height and radius of pile of powder using Eq. (3)[18, 19].

$$\theta = \tan^{-1}(h/r) \quad (3)$$

Where, θ–angle of repose, °

h–height of pile, cm

r– radius of pile, cm.

2.2.4 Carr's index (CI)

Powder flow properties are indicated by Carr's index (% compressibility index). It is calculated by using Eq. (4)[18, 19].

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (4)$$

2.2.5 Hausner ratio (HR)

It is an indirect index of flow. Lower the Hausner ratio (< 1.25) value indicates better flow properties of blend [18, 19]. It was calculated by the following E-/5)

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

(5)

2.3 Manufacturing of Pregabalin ER Tablets

Core tablets of Pregabalin were compressed by using 16 station compression machine (Cadmach- CMD3, India) using 12 mm, standard concave, round plain punches. The F1 to F8 formulations were designed using different concentrations of Mannitol, PEG and Cellusoe acetate to check its impact on the physical parameters of the tablet. Further these formulation were coated by using extended release polymer and plasticizer or pore former by using tablet coater (Ganscota- Gansons, India). These extended release tablets further drilled by using drilling machine (Scantech- Protab Scale Drilling Laser System)

2.4 Evaluation of Pregabalin ER tablets

2.4.1 Diameter and thickness:

Randomly selected three tablets from each formulation and their diameter and thickness were measured using digital vernier caliper (Mitutoyo Products, Japan)[21].

2.4.2 Hardness:

Randomly selected three tablets from each formulation were taken and their hardness was determined using Lab India hardness tester [21].

2.4.3 Weight variation test:

Randomly selected 20 tablets were weighed and their average weight was determined (Digital Analytical Balance Mettler ME204)[21].

2.4.4 Friability:

Percent friability of the tablets was determined using Electrolab friabilator (Navi Mumbai, India). Previously weighed 20 tablets were placed in the drum and this was rotated at the speed of 25 rpm for 4 min ie 100times. The tablets were removed, dedusted and accurately weighed [21] . This was considered as final weight of the tablets. The percent friability w

$$\text{Friability (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (6)$$

2.4.5- Orifice Diameter:

Extended release coated tablets were further drilled by using laser drilling machine and appropriate orifice diameter determined by using scale loupe (Navkar Impex). Orifice diameter on the tablets surface is one of the decisive parameter in the development of osmotically controlled oral drug delivery system because it will have direct relationship with amount of drug release during In-vitro and In-vivo study of the formulation. Extended release coated tablets were drilled with different orifice diameter ie 0.5mm, 0.6mm, 0.7mm and 0.8mm to optimize the range of diameter of orifice.

2.4.6 Drug content:

Preparation of Standard: Accurately weigh and transfer 80mg of Pregabalin working standard in to 200mL volumetric flask and add 150mL of diluents and sonicate to dissolve. Dilute up to the mark with diluents and mix well. Fliter the solution through 0.45µ Nylon Syringe filter. Fill the HPLC vial.

Preparation of Sample solution: Accurately weigh NLT 20 tablets and determine the average weight. Crush the tablets to fine powder. Accurately weigh and transfer tablet powder equivalent to 400mg of Pregabalin in to a

clean and dry 1000mL volumetric flask and immediately add about 600mL of diluents, swirl to disperse the sample. Sonicate the sample for 20mins at 25°C with vigorous intermittent shaking then stir for 10mins on magnetic stirrer. Dilute up to the mark with with diluent. Centrifuge at 10mins for 4000rpm. Filter the supernatant through 0.45µ Nylon Syringe filter. Fill the HPLC vial.

Procedure: Separately inject 50µL of blank, standard solution and bracketing standard in to chromatographic system and record the chromatograms.

2.4.7 In-vitro dissolution studies

The in-vitro dissolution studies of prepared tablets were conducted in USP dissolution test apparatus type II (DS, 14000 SMART, Lab India, India)using 900 ml of 0.06 N HCL at 37 ± 0.5°C temperature and 50 rpm paddle speed for 1, 2, 4, 6, 8, 10, 12, 16 and 24 hr. The tablets were placed into the dissolution vessel when temperature reached to the 37 ± 0.5°C. At predetermined time interval 5 ml of samples was withdrawn from the dissolution medium and replaced with fresh medium to maintain the constant volume. After filtration of each aliquote through 0.45 µ Nylon syringe filter and fill in HPLC vial. Separately inject 50µL of blank, standard solution, sample solution and bracketing standard solution in the HPLC chromatographic system and record the chromatograms. The dissolution data obtained was plotted between percent cumulative drug dissolved and time[25]. The comparative drug release of the product for all the nine formulations is as per the Table------

2.4.8 Stability study:

The tablets of optimized formulation of Pregabalin ER Tablets (OROS) were packed in thick walled 100CC HDPE bottles and sealed with 38mm propylene child resistant closure, 30 Tablets each were packed in each bottle. The Stability study was planned for 3 and 6 months time interval at 40± 2°C /75% ± 5% RH and at 25± 2°C /60% ± 5% RH to understand the trend of the dissolution data. These HDPE bottles were kept in the stability chamber (Remi Laboratory Instrument CHM-6S [GMP]).The tablets were evaluated for any changes in physical parameters as well as in the drug release profile of the formulations kept on stability.

Dissolution results of initial and stability results 3M and 6M were compared to understand the impact on the drug release during stability of the optimized formulation. The physicochemical data of the Initial and stability samples is given as below.(Table) The plot of percentage drug release against time (hr) on the day of preparation of tablets and after 3 months for stability study was plotted[27].

3 Results and discussion

3.1 In process parameters of the blend of all trials

The blend properties like angle of repose, bulk density, tapped density, Carr's index and Hausner ratio were recorded [Table 2]. The values of angle of repose, bulk density, tapped density; Carr's index and Hausner ratio of powder blend were found to be in the range of 21.6 to 23.53, 0.40 to 0.45, 0.46 to 0.51, 10.638 to 15.68 and 1.14 to 1.186 respectively. The values of angle of repose, Carr's index and Hausner ratio were shows that the powder blends have good flow property and compressibility.

Table 2: In process parameters of the blend

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner ratio	Angle of repose (°)
F1-330	0.43± 0.03	0.5 ±0.04	14 ±1.22	1.163 ± 0.01	21.6 ± 1.85
F2-330	0.45 ± 0.04	0.51 ±0.05	11.765 ±0.68	1.133 ±0.00	22.65 ± 1.89

F3-330	0.42 ± 0.03	0.48 ±0.07	12.5 ±1.4	1.143 ±0.02	23.53 ± 2.33
F4-330	0.4 ± 0.05	0.46 ±0.04	13.043 ±1.6	1.15 ±0.01	22.31 ±2.81
F5-330	0.4 2± 0.04	0.47 ±0.04	10.638 ±1.7	1.119 ±0.02	22.24 ±2.64
F6-330	0.42 ± 0.06	0.48 ±0.05	12.5 ±1.34	1.143 ±0.02	23.64 ±2.2
F7-330	0.43 ± 0.05	0.51 ±0.06	15.68 ±0.90	1.186 ±0.00	22.68 ±3.24
F8-330	0.42 ± 0.03	0.49 ±0.05	14.286 ±2.1	1.167 ±0.02	22.34 ± 2.62
F9-330	0.43 ± 0.04	0.49 ±0.03	12.244 ±1.62	1.14 ±0.01	22.63 ±2.66

Where,All the values were expressed as Mean of triplicate evaluation (n=3).

3.2 Physicochemical evaluation of tablets

The tablets were evaluated for physicochemical characterizations and their observations were recorded in [Table 3].

Table 3: Physicochemical characteristics of tablets

Formulation	Diameter[a] (mm)	Thickness[a] (mm)	Weight[b] (mg)	Hardness[a] (N)	Friability[b] (%)	Orifice diameter[b] (mm)	Drug content[b] (%)
F1-330	12.02	6.85	771.2	120.5	0.23	0.63	98.9
F2-330	12.00	6.88	770.3	127.8	0.21	0.65	99.2
F3-330	12.01	6.81	769.4	126.9	0.25	0.60	100.2
F4-330	12.03	6.92	768.36	131.1	0.26	0.58	100.5
F5-330	12.04	6.86	770.5	127.6	0.19	0.64	99.6
F6-330	12.02	6.88	771.2	123.8	0.22	0.61	98.8
F7-330	12.02	6.84	772.1	128.3	0.16	0.60	97.6
F8-330	12.01	6.88	770.25	125.4	0.13	0.62	99.9
F9-330	12.02	6.85	768.9	122.5	0.18	0.64	99.2
F9S-330 (3M-ACC)	12.02	6.86	769.5	NR	NR	NR	100.1
F9S-330 (6M-ACC)	12.02	6.82	770.1	NR	NR	NR	99.12
F9S-330 (6M-RT)	12.02	6.84	771.1	NR	NR	NR	98.6
Physicochemical Parameters of tablets with different orifice diameter							
F9-330-1	12.02	6.85	768.9	122.5	0.18	0.51	99.2
F9-330-2	12.02	6.85	768.9	122.5	0.18	0.70	99.2
F9-330-3	12.02	6.85	768.9	122.5	0.18	0.79	99.2

Where, F9S indicates stability batch. All values were expressed as mean and [a]indicate sample size (n=3) and [b] indicate sample size (n=20). NR- Indicates not required for coated tablets.

The diameter of Pregabalin ER Tablets was ranging from 12.00 to 12.44mm (Limit- 12.00± 0.1mm) The thickness of Pregabalin ER Tablets was ranging from 6.81 to 6.92mm (Limit- 6.8± 0.3mm). The hardness of tablets was found ranging from 120.5 to 128.3N (Limit: 125N ±25N). The average weight of Pregabalin ER tablets was

ranging from 768.36 to 772.1mg (Average weight as per USP-769.2 ±3%). The percentage friability of Pregabalin ER tablets was found in the range of 0.13 to 0.26% (Limit as per USP- NMT 1%). The drug content in the tablets was ranging from 97.6 to 100.5 (*Assay Limit as per USP- 90-110% of labeled amount). The values of orifice diameter were ranging in between 0.58mm to 0.65mm (Limit based on dissolution data: 0.6 ± 0.1mm). All tablet formulations passes the pharmacopoeial tests according to United States Pharmacopoeia. (*Assay limits are taken from monograph USP forum of Pregabalin Capsules).

Extended release coated tablets from batch No- F9330 were used for optimization orifice diameter. These tablets were drilled for different orifice diameters ie 0.5mm, 0.6mm, 0.7mm & 0.8mm to evaluate the impact of orifice diameter on the drug release of the formulation.

3.3 In-vitro dissolution studies: Fig. 1 indicates that the drug dissolution from Pregabalin ER tablets prepared by varying the concentration of key ingredients to check the role drug release of the product. There are 08 different permutation combinations of these three ingredients were evaluated with two levels.

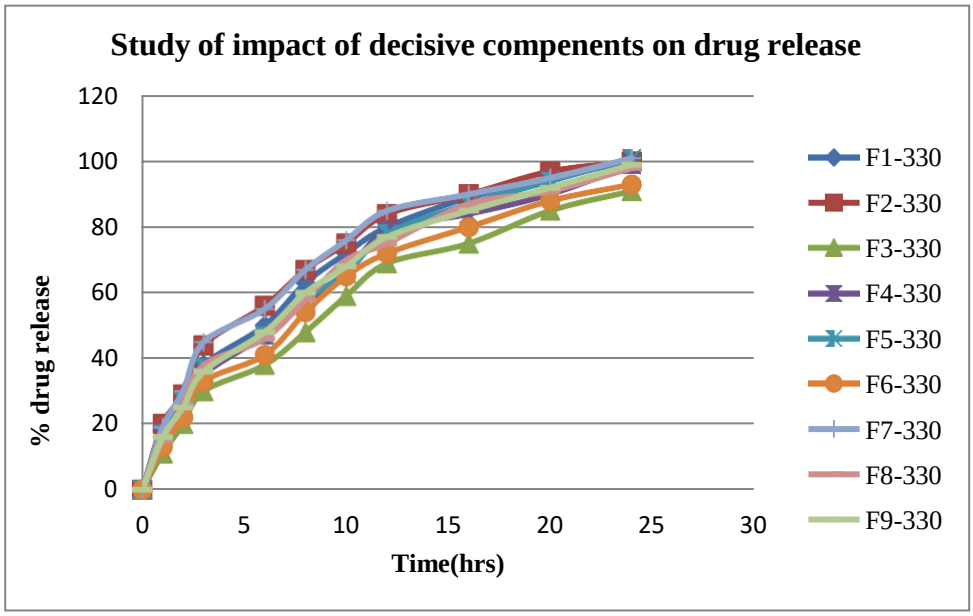

Fig.1 Study of impact of decisive components on drug release of Pregabalin ER Tablets 330mg

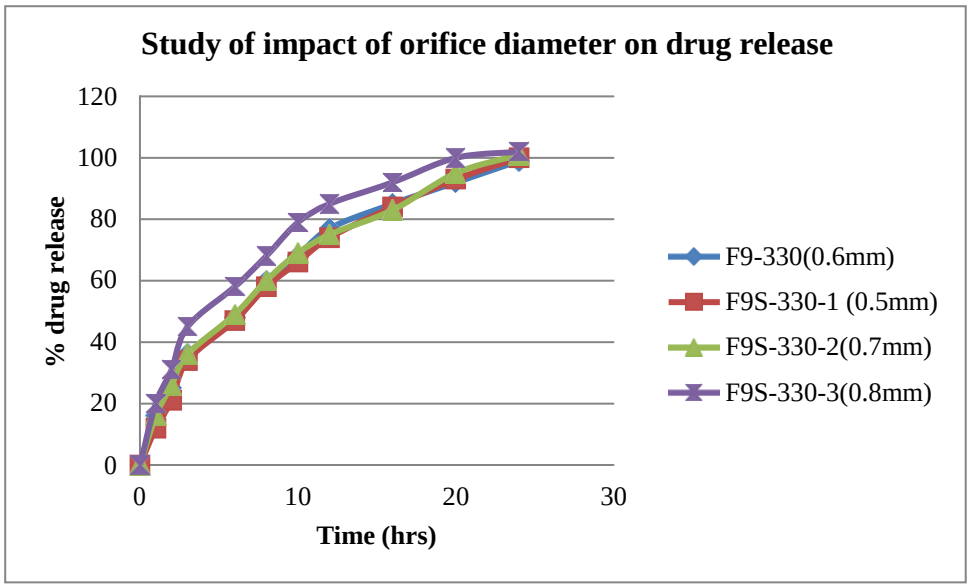

Fig. 2 Study of impact of orificediameter on drug release of Pregabalin ER Tablets 330mg

3.4 Kinetic analysis:

3.5 Stability studies

The optimized formulation was charged on stability at accelerated and long term conditions up to 6months. These samples are evaluated for physical parameters and drug release profile at 3M and 6M condition during stability study. [Tables 3], [Table 4] and[Fig. 3].

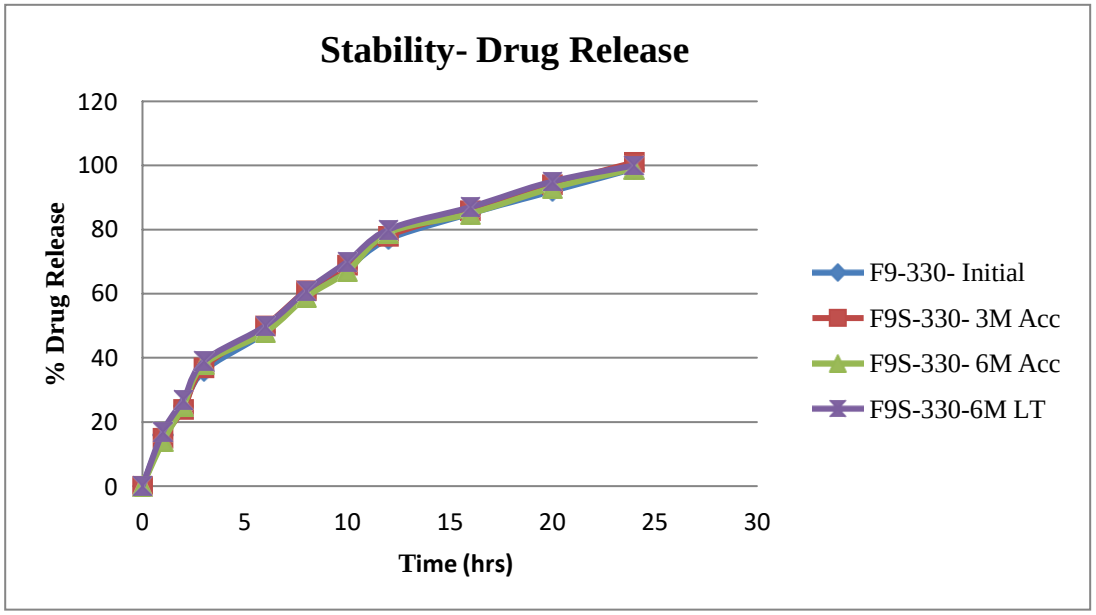

Fig. 3 Comparative drug release profile of optimized formulation stability batch at accelerated and long term condition.

4. Conclusions

The gastroretentive Pregabalin Extended release Tablets were successfully designed with different formulation variables. The excipient which impacts the dissolution profile were identified. The formulation were manufactured with different concentrations of these excipient and its impact on the physical and chemical parameters of the product was evaluated.

1. Drug release of formulation contains lower amount of ER coating and higher amount of pore forming agent (F2-330 & F7-330) found to be slightly faster as compared with optimized formulation drug release.(F9-330)
2. Drug release of formulation contains higher amount of ER coating and lower amount of pore forming agent (F6-330) found to be retarded as compared to optimized formulation drug release.(F9-330)
3. Drug release of the remaining formulations found to be comparative with optimized formulation.(F9-330)
4. As per the drug release data of all formulations it was clear that, concentration of cellulose acetate and polyethylene glycol plays greater role in the drug release although concentration mannitol least impacted the dissolution .
5. Orifice diameter of the tablet identified as critical process parameter because it has played crucial role in the drug release of the extended release of the Pregabalin Tablets. Based on the drug release pattern

different we have restricted the diameter of orifice on the tablet ie 0.6mm ± 0.1mm. Beyond these levels it impacts the drug release of the product.

6. Physical and chemical parameters evaluated during stability products found comparable with initial data of the formulation. This indicates the optimized formulation is stable up at 6M accelerated and 6M long term conditions.

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