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Research Article

Development Optimization and Evaluation of Fast Disintegrating Tablets of Antiepileptic Drug Carbamazepine

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Abstract:

Background: The main objective of present research work is to formulate the Carbamazepine as Fast Disintegrating tablets to give fast relief and an increase in the patient compliance. Carbamazepine, an antiepileptic, belongs to BCS Class-II and used to control some types of seizures in the treatment of epilepsy and Neuropathic Pain by blocking use-dependent sodium channels.

Methods: The powdered materials were compressed by direct compression technique using super disintegrants like sodium starch glycollate, croscarmellose sodium and starch, Magnesium Stearate and Di Calcium Phosphate are used as lubricant and diluents/fillers respectively.

Result and Discussion: Totally nine formulations were designed and are evaluated for hardness, friability, thickness, assay, wetting time, Disintegration time, in-vitro drug release. From the Results concluded that all the formulation were found to be with in the Pharmacopeial limits and the In-vitro dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. The optimized formulation was characterized with the help of Differential Scanning Calorimetry (DSC), and Fourier Transform Infrared Spectroscopy (FTIR) studies show no interaction between the drug and the excipients. The stability study was conducted as per the ICH guidelines and the formulations were found to be stable, with insignificant changes in hardness, drug content and disintegration time.

Conclusion: These results revealed that fast disintegrating tablets of the poorly soluble drug, carbamazepine, showing enhanced dissolution and, hence, better patient compliance.

Keywords: Carbamazepine, Fast Disintegrating Tablets, Croscarmellose Sodium, Sodium starch glycolate, Disintegrating time, Direct compression.

Introduction

For the past four decades, there has been enhanced demand for more patient compliance dosage forms. As a result, the demand for their technologies has been increasing annually. Since the development cost of a new chemical entity is very high,

the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects[5-6].

Dysphagia (difficulty in swallowing) is common among all age groups and more specific with paediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications[1,2]. Other categories that experience problems in using conventional oral dosage forms include the mentally ill, motion sickness, sudden episodes of allergic attack or coughing. Sometimes, it may be difficult to swallow conventional dosage form due to non-availability of water. To ensure safety during oral medication administration, patients with dysphagia require an appropriate oral dosage form or modification of the dosage form, the development of a novel type of solid oral dosage form called mouth-dissolving tablets or fast dissolving tablets which disintegrate and dissolve rapidly in saliva without the need of drinking water. The disintegration time for good MDTs varies from several seconds to about a minute[3,4].

Epilepsy can occur at any age, from paediatrics to geriatrics but it is highly associated with percentage of aged population of a country. Drugs such as Carbamazepine were selected as they are used as 1st line therapy for the treatment of various types of epilepsy.

Carbamazepine (CBZ) is an antiepileptic and anxiolytic drug widely used to treat seizures, trigeminal neuralgia and bipolar disorders. The anticonvulsant activity of CBZ results from blockage of sodium channel activity thereby modulating release of excitatory neurotransmitters. CBZ shows its anxiolytic activity by modulating adenosine mediated neurotransmitters to alter postsynaptic ionic current.[5] Hence in the present study, the increasing trend of dysphagia and epilepsy or seizures incidence in paediatrics, adults and geriatrics has led to the development of new pharmaceutical preparations such as fast disintegrating tablets or fast dissolving tablets incorporating antiepileptic agents. These formulations were formulated, optimized and evaluated. Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and the ODTs formed vary in various properties such as, mechanical strength of tablet, taste and mouth feel, swallowability, drug dissolution in saliva, bioavailability and stability. Various processes employed in formulating FDTs include Freeze-Drying or Lyophilization, cotton candy process, molding, spray drying, mass extrusion and compaction (wet granulation, dry granulation, direct compression).[6] In the present study the direct compression method was adopted to manufacture the FDT tablets, since it is very simple and do not require any sophisticated equipment's. The direct compression represents the simplest and most cost-effective tablet manufacturing technique.

Criteria for Fast Disintegrating Drug Delivery System[7]

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be harder and less friable.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipment's at low cost.

Criteria for excipient used in the formulation of FDTs[8]

- It must be able to disintegrate quickly.
- Their individual properties should not affect the FDTs.
- It should not have any interactions with drug and other excipients.
- It should not interfere in the efficacy and organoleptic properties of the product.
- When the final integrity and stability of the product.

The melting points of excipients used will be in the range of 30-35^{0}C.

Drug Profile

Carbamazepine, a dibenzapine derivative with structure resembling the tricyclic antidepressants, is used to control some types of seizures in the treatment of epilepsy. One of the major problems with this drug is its very low solubility in biological fluids and its biological half-life between 18 to 65 h that results into poor bioavailability after oral administration[9-10]. Carbamazepine increases latency, decreases responsivity and suppress the polysynaptic pathway associated with cortical and limbic function. It also reduces post –tetanic potentiation. It is a Na + channel blockers that slows that slow the rate of recovery of Na+ channel from the inactivated state to closed state. This has the effect of suppressing a seizure focus as well as preventing rapid spread of activity from the seizure. The absorption of CBZ following oral administration has been shown to be slow, erratic, unpredictable but almost complete with CBZ is lipid soluble compound, which is slowly and variably absorbed from the GIT. The slow and discontinuous absorption of CBZ from the gastrointestinal tract (GIT), and subsequent variable plasma concentrations, has been attributed in part to the slow dissolution rate of CBZ in GIT fluids or through a rapid GIT transit time through the anti-cholinergic effects of CBZ. It is therefore likely, that the absorption of CBZ is primarily dissolution-rate limited.

Table 1: Composition of Various Formulations of Carbamazepine Fast disintegrating Tablets

Formulation (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carbamazepine	200	200	200	200	200	200	200	200	200
Starch	10	5	5	10	7.5	5	5	10	10
Sodium starch glycolate	10	30	10	30	20	10	30	30	10
Croscarmellose Sodium	30	30	10	10	20	30	10	30	10
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Di Calcium Phosphate	92	77	117	92	94.5	97	97	72	112
Talc	4	4	4	4	4	4	4	4	4
Total weight of Tablet	350	350	350	350	350	350	350	350	350

Table 2: Post-Compression Parameters for the Formulations

Formulation Code	Thickness (mm)	diameter (mm)	Hardness (Kg/Cm2)	Friability (%)	Weight variation (mg)	Wetting Time (Sec)	Disintegration Time (s)	Drug Release after hour	Drug Content (%)
F1	5.21	9.7	3.5	0.6	353	15.26	25	98.84	99.45
F2	5.24	9.7	4.2	0.51	354	33.13	50	96.58	99.28
F3	5.22	9.7	3.4	0.62	354	33.44	42	95.33	99.41
F4	5.21	9.7	3.4	0.64	352	16.44	27	97.33	99.53
F5	5.23	9.7	3.8	0.67	354	40.25	53	96.18	99.39
F6	5.25	9.7	4.1	0.54	354	33.54	50	95.20	99.92
F7	5.23	9.7	3.9	0.6	354	32.25	46	96.84	99.23
F8	5.24	9.7	3.5	0.59	354	16.24	35	99.02	99.51
F9	5.22	9.7	3.7	0.65	355	16.23	20	98.84	99.49

Evaluation of Carbamazepine Fast disintegrating tablets:

Hardness[11]: Hardness is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The hardness was measured using Monsanto Hardness tester. The values were expressed in Kg/cm^2.

Weight variation: Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablets was noted. Average weight was calculated and the individual weights were compared with the average weight. The weight of not more than two tablets must not deviate from the average weight by more than 5%.

Wetting Time: A glass Petridish was partially filled with water and tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from lower surface of the tablet. Time required for water to reach the center of upper surface of tablet was noted as wetting time.

Friability [11]: The initial weight of 20 tablets was recorded and the tablets were placed in a Roche friabilator and rotated at a speed of 25 rpm for 100 revolutions. The tablets were then removed from the friabilator, fines were dusted off, and the weight was recorded. Percentage friability was calculated by using the formula:

Percentage Friability = [(Initial Weight – Final Weight)/ Initial Weight] × 100

Disintegration time[13-14]: Disintegration of fast disintegrating tablets were determined by using ‘‘Electrolab Disintegration Tester” Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined.

In Vitro Dissolution Studies[12]: Dissolution testing was performed in an "Electrolab Dissolution Tester, Germany" using Apparatus 1 (Basket method) at 100 rpm. Six tablets were evaluated per formulation in this study. The dissolution medium was 900ml distilled water with 1% sodium lauryl sulphate (USP method) in 37.0 ± 0.5ºC. The amount of drug present was determined according to the USP monograph for carbamazepine tablets using UV spectrophotometer testing at 284nm.

Drug Content Estimation[11]: Drug content was determined by weighing randomly selected tablets, pulverizing to a fine powder. The powder equivalent to 10 mg Carbamazepine was weighed and dissolved in 10 ml of methanol in volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with Phosphate buffer pH 6.8and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml Phosphate buffer pH 6.8 in separate volumetric flask. The drug content in was determined spectrophotometrically at 285 nm.Stability Analysis: The formulation F8 was subjected to stability studies, by storing at 40^o ±2^{o}C/75±5%RH for a period of 30 days. At the optimized period, samples were analysed for drug content, disintegration time and in vitro dissolution studies.

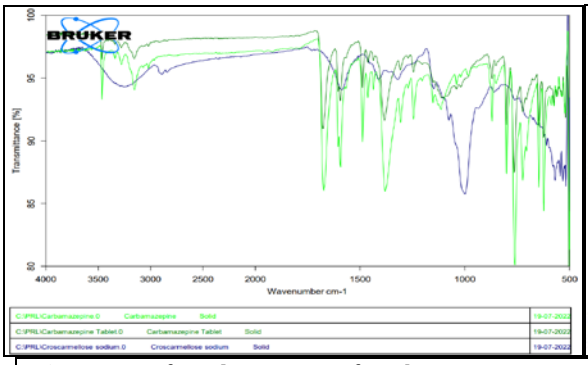

Figure 1: Infrared spectrum of Carbamazepine, Carbamazepine tablet & Croscarmellose sodium

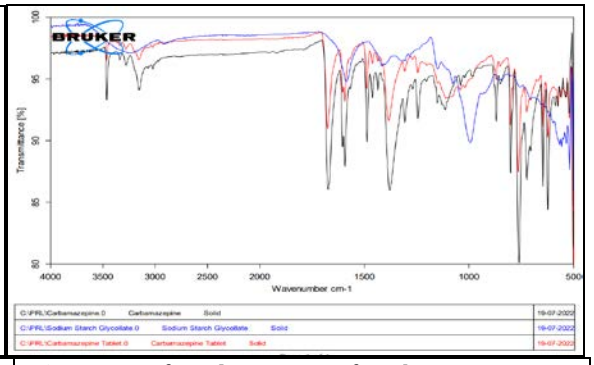

Figure 2: Infrared spectrum of Carbamazepine, Carbamazepine Tablet & Sodium Starch Glycolate

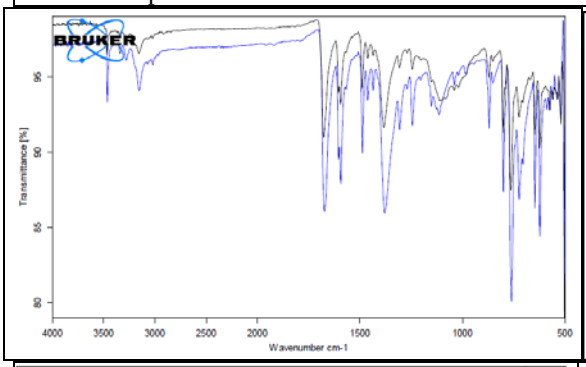

Figure 3: Infrared spectrum of Carbamazepine pure drug and Carbamazepine Tablets Comparison Profile

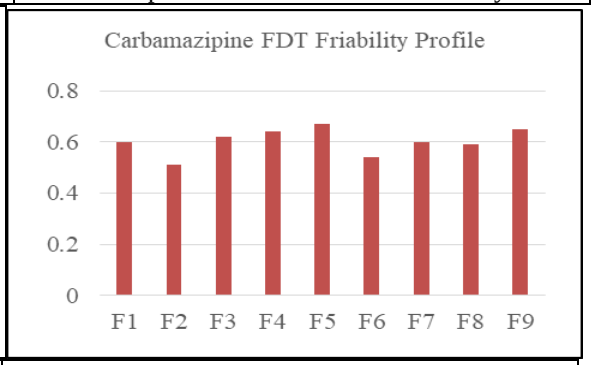

Figure 4: Carbamazepine FDT Friability Profile

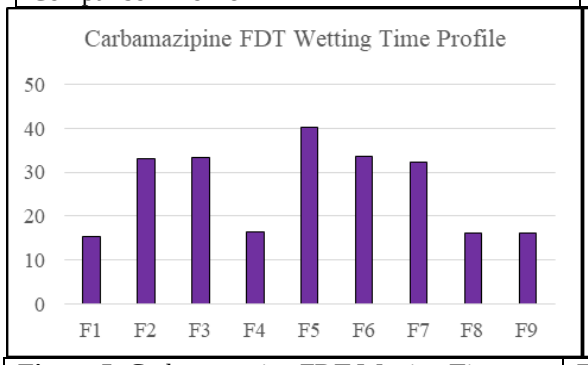

Figure 5: Carbamazepine FDT Wetting Time Profile

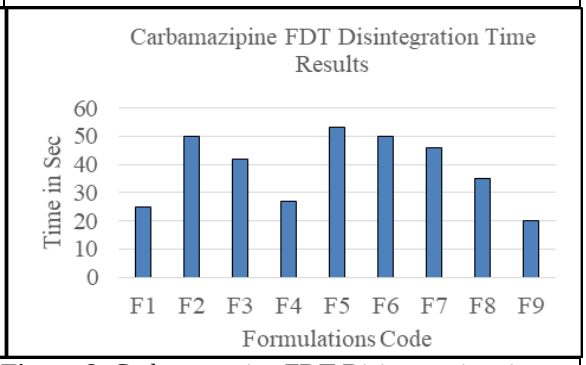

Figure 6: Carbamazepine FDT Disintegration time

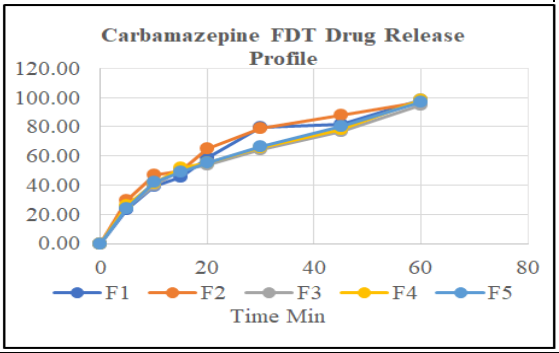

Figure 7: Comparative dissolution profile of Carbamazepine FDT F1 to F5

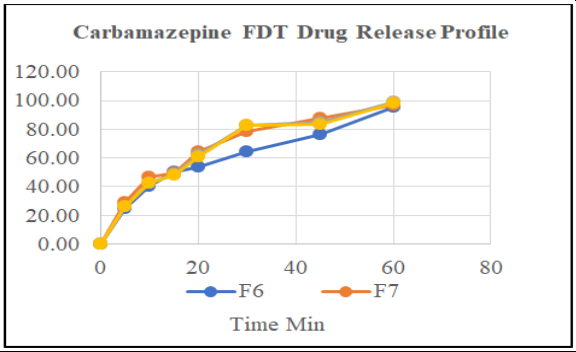

Figure 8: Comparative dissolution profile of Carbamazepine FDT F6 to F9

Result & Discussion:

Because the frequency of vibrations within a chemical structure is very sensitive to how the atoms are arranged and how the atoms interact with neighboring functional groups, not only can FTIR provide a detailed fingerprint of pharmaceutical substances of different physical forms, but also it can detect changes in hydrogen-bonding pattern of amorphous materials.

Infra-red spectrum of drug Carbamazepine FDT and Excipients were recorded over KBr disc method and obtained spectra were shown in the figure. In pure drug Carbamazepine FDT, the characteristic absorption band at 3464 cm−1 was due to the stretching vibration of N-H group. The absorption band at 1673 cm−1 was due to the -CO-R- group, -C=C- and -C=O symmetric band at 1593 cm -1 and (-NH) deformation vibration at 1380 cm-1. This further confirms the purity of Carbamazepine FDT. All the characteristic peaks of Carbamazepine were present in the spectrum of drug and excipients mixture, indicating compatibility between drug and excipient. Hence, IR spectrum concluded that there was no significant change in the chemical integrity of the drug.

All the prepared tablets were evaluated for different post compression parameters, drug content, mean hardness, friability, mean thickness, Weight variation as per official methods and results are given in Table 2. The hardness of tablets was in the range of 3.5-4.2 Kg/cm^2. Weight loss in the friability test was not more than 0.67%. Drug content of prepared tablets was within acceptance range only. The Wetting Time of tablets was in the range of 15.26 – 40.25 sec. The Disintegration Time of tablets was in the range of 20-42 seconds. Results for all Post-compression parameters were tabulated or shown in Table 2. In vitro Dissolution testing was performed in an "Electrolab Dissolution Tester, Germany" using Apparatus 1 (Basket method) at 100 rpm. Six tablets were evaluated per formulation in this study. The dissolution medium was 900ml distilled water with 1% sodium lauryl sulphate (USP method) in 37.0 ± 0.5ºC. The amount of drug present was determined according to the USP monograph for carbamazepine tablets using UV spectrophotometer testing at 284nm. The In-vitro dissolution profiles of tablets are shown in Fig.7 & 8 and the dissolution parameters are given in Table 2. Cumulative % Drug release of Factorial Design Formulations F1 -F9 at 1 Hr were found to be in the range of 95.34-99.84%. From the result it reveals that the release rate was higher for formulations containing high level of Sodium starch glycolate/ Croscarmellose sodium compared with other Formulations containing Lower level, due to High concentration of Superdisintegrant in combination, shows various disintegration mechanism such as wicking and swelling etc. more compared with lower concentration and alone, drug may release rapidly and shows improved bioavailability. Therefore, required release of drug can be obtained by manipulating the composition of Sodium starch glycolate and Croscarmellose sodium.

Release Kinetic Studies[15-16]:

To study the drug release kinetics, the dissolution data of all formulations were fitted to zero order, first order, Higuchi model, and Korsmeyer- Peppas model.

In practise, it is frequently observed that the linear relationship between the amount of drug liberated and the square root of time is only true in a portion of the drug's dissolution curve.

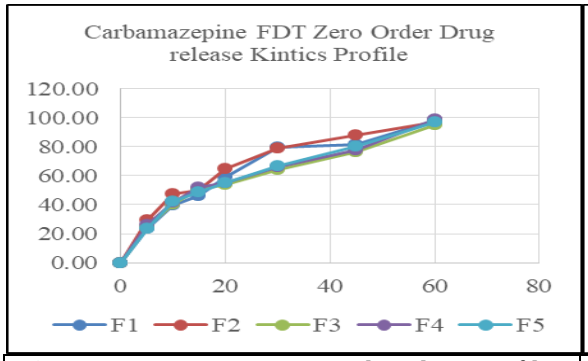

Figure 9: Comparative Zero Order release profile of formulations F1 to F5

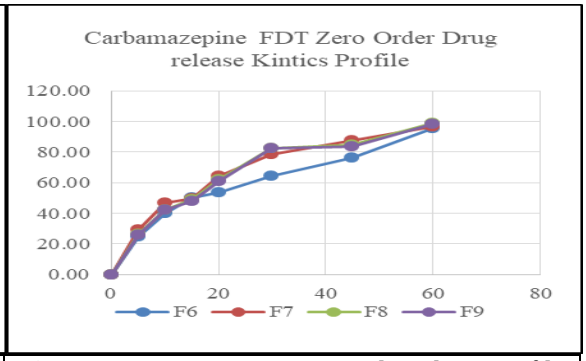

Figure 10: Comparative Zero Order release profile of formulations F6 to F9

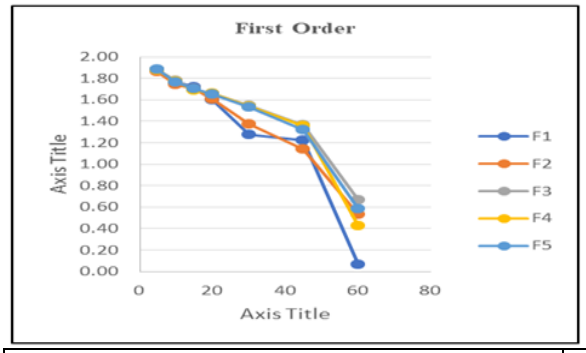

Figure 11: Comparative First Order release profile of formulations F1 to F5

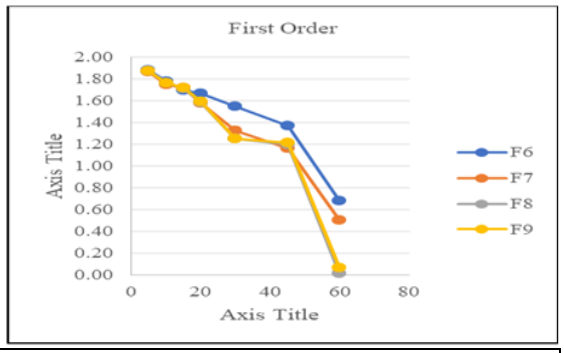

Figure 12: Comparative First Order release profile of formulations F6 to F9

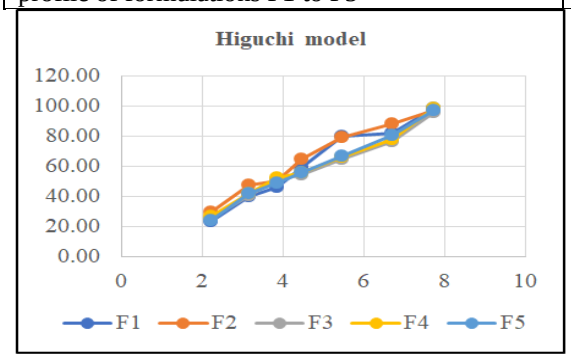

Figure 13: Comparative Higuchi release profile of formulations F1 to F5

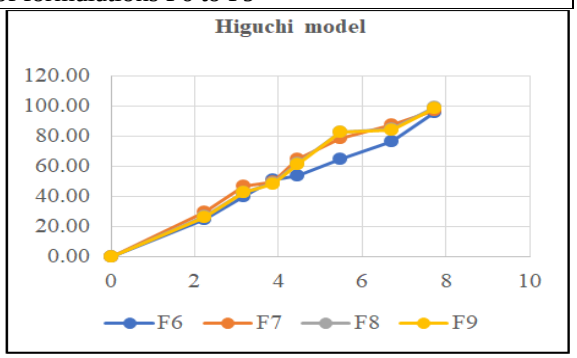

Figure 14: Comparative Higuchi release profile of formulations F6 to F9

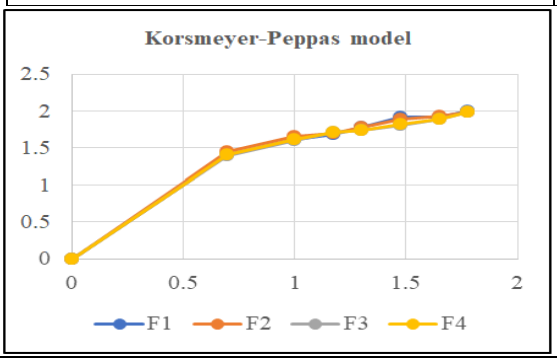

Figure 15: Comparative Korsmeyer/Peppas release profile of formulations F1 to F4

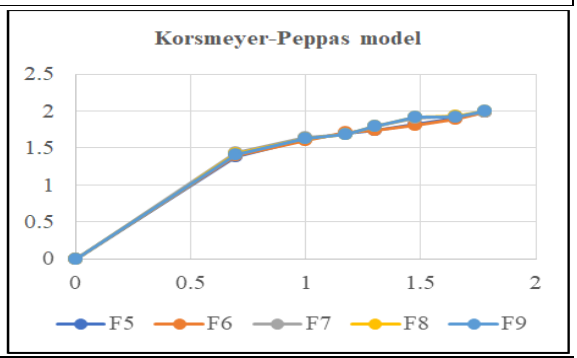

Figure 16: Comparative Korsmeyer/Peppas release profile of formulations F5 to F9

Stability Studies Results: The optimized formulation tablets are to be subjected to Stability Studies. The tablets were stored at 40^0 C / 75% RH and room temperature in a closed high density polyethylene bottle for three months. The bottles are properly labelled and the kept for three months under these conditions and evaluated for appearance, disintegration time, % drug content and % drug release. The stabilized tablets are checked for their appearance and color in this parameter. The color and appearance were recorded. Initially the tablets of all nine batches were white in color. The optimized tablets were subjected to disintegration time test to check for any changes in their disintegration times. The USP Disintegration Test Apparatus was used to carry out this test. The stability test was carried out on the optimized formulations only, which are those with the best evaluation parameters. Short term stability study was conducted for optimized formulation for the period of three months. Optimized formulation was selected based on in-vitro drug release study. F10 formulation was selected for optimization.

Table 3: Stability testing of F10 formulation

Stability Testing of F10 Formulation			
Time	Initial	1st Month	3rd Month
0	0.00	0.00	0.00
5	27.21	26.66	30.05
10	44.73	40.38	48.66
15	54.98	51.11	57.14
20	69.79	62.94	71.77
30	82.95	78.32	85.63
45	92.40	90.87	91.05
60	97.91	97.77	98.92

Summary and Conclusion

From the results it was clearly understand that as the concentration of Superdisintegrant increases the release rate of drug was RAPID (Improved Solubility) and both of these Superdisintegrants can be used in combination since do not interact with the drug which may be more helpful in achieving the desired fast Disintegrating of the dosage form for rapid action and improved Bioavailability. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be Non-Fickian Diffusion, first order release type. The optimized formulation F10 was selected for short term accelerated stability studies for the period of 3 months. On the basis of the optimized formulation F9 may be used for the effective management of Epilepsy, convulsions, Tremors and Neuropathic Pain. This may improve the patient compliance by showing rapid action via disintegration without difficult in swallowing and side effects which will ultimately improve the therapeutic outcome. We would be able to minimize the per oral cost.

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