EFFECT OF DIFFERENT CONCENTRATIONS OF SUPERDISINTEGRANTS OF GABAPENTIN TABLETS

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Gabapentin is an anti-epileptic drug used in the treatment of Epilepsy. It is a water soluble drug with bioavailability of 100% and plasma half-life 5 to 7 hrs. Gabapentin tablets with various superdisintegrants were developed as oral drug delivery systems to enhance safety, efficacy of the drug molecule and to achieve better patient compliance. In the present investigation, Gabapentin tablets were formulated by wet granulation by incorporating various concentrations of superdisintegrants. The *in vitro* studies indicated that the drug release of optimized formulations viz. Trail 1, 2, and 3 exhibited the rank order of Trail 3 < Trail 1< Trail 2 (90.73< 98.4 < 98.63).Trail 1 formulation showed sufficient rheological and tableting parameters with high release rate 98.63%. Hence it could be considered as the optimized wet granulated tablet formulation with crospovidone IG (3.3%) exhibited desired immediate drug release property.

KEYWORDS : Gabapentin, Anti epileptic, Superdisintegrants , Crosspovidone

INTRODUCTION

Recent advances in novel drug delivery systems aimed to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, creams, capsules, pills, suppositories, aerosols, ointments, liquids, and injectables as drug carriers[1].

Among these all parentral route suffers disadvantage like frequent pain and discomfort of injection with all physiological fears associated with the needle. Oral drug delivery has been known for centuries as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason behind that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration, the drug is as well absorbed as the food stuffs that are ingested daily[2].

Superdisintegrants:

Disintegrants are substances or mixture of substances added to tablet formulations to promote the break-up of the tablet (and capsule "slugs') into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. Tablet disintegration has received considerable attention as an essential step in obtaining faster drug release. The emphasis on the availability of the drug highlights the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited

drug dissolution behaviour. A number of factors affect the disintegration behaviour of tablets. The development of fast dissolving or disintegrating tablets provides an opportunity to take into account the role of disintegrants. Recently, chemically modified disintegrants termed as superdisintegrants have been developed to improve the disintegration processes. Selection of appropriate formulation excipient and manufacturing technology can obtain the design feature of fast disintegrating tablet. The disintegrants have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet[3,4].

Selection of superdisintegrants:

Since superdisintegrant is used as an excipient in the tablet formulation, it has to meet certain criteria other than its swelling properties. The requirement placed on the tablet disintegrant should be clearly defined.

The ideal superdisintegrant should have following properties:

1. Poor solubility.
2. Poor gel formation.
3. Good hydration capacity.
4. Good moulding and flow properties.
5. No tendency to form complexes with the drugs.
6. Good mouth feel.
7. It should also be compatible with the other excipients and have desirable tableting properties.

Although some are better than others, the currently marketed superdisintegrants exhibit an optimum combination of properties

Method of addition of superdisintegrants:

There are three methods of incorporating disintegrating agents into the tablet.

- Internal addition
- External addition
- Internal and External addition

Internal addition:

In wet granulation method, the disintegrant is added to other excipients before wetting the powder with the granulating fluid. Thereby, the disintegrant is incorporated within the granules. In dry granulation method, the disintegrant is added to other excipients before compressing the powder between the rollers. In a computer optimized experiment, the study show the effect of incorporating a disintegrant, croscarmellose sodium, intragranularly, extra granularly or distributed equally between the two phases of a tablet in which a poorly soluble drug constituted at least 92.5% of the formulation. The results analyzed by means of a general quadratic response surface model suggest that, tablets with the same total concentration of croscarmellose sodium dissolve at a faster rate when the super disintegrant is included intragranularly. Tablet friability is not affected by the method of disintegrant incorporation[5,6,7] .

External addition:

In both wet and dry granulation method, the Superdisintegrant is added to the granules during dry mixing prior to compression. The effect of mode of incorporation of superdisintegrants (croscarmellose sodium, sodium starch glycolate and crospovidone) on dissolution of three model drugs with varying aqueous solubility (carbamazepine, acetaminophen and cetrizine Hcl) from their respective tablet formulations by wet granulation was studied. It is

proved that crospovidone is effective in improving the dissolution of the drugs in extra granular mode of addition seems to be the best mode of incorporation, irrespective of the solubility of the main tablet component[8,9] .

Internal and external addition:

In this method, disintegrant is divided into two portions. One portion is added before granule formation (intra) and remaining portion is added to granules (extra) with mixing prior to compression. This method can be more effective. If both intragranular and extra granular methods are used, extra-granular portion break the tablet into granules and the granules further disintegrate by intra-granular portion to release the drug substance into solution. However, the portion of intra-granular disintegrant (in wet granulation processes) is usually not as effective as that of extra-granular due to the fact that it is exposed to wetting and drying (as part of the granulation process) which reduces the activity of the disintegrant. Since a compaction process does not involve its exposure to wetting and drying, the intragranular disintegrant tends to retain good disintegration activity[10,11] .

Mechanism of disintegrations by superdisintegrants:

There are five major mechanisms for tablet disintegration as follows:-

1. Swelling
2. Porosity and Capillary action (Wicking)
3. Deformation
4. Due to disintegrating particle/particle repulsive forces
5. Heat of wetting
6. Due to release of gases
7. Enzymatic reaction
8. Combination action

AIM AND OBJECTIVES

Solid oral dosage forms such as tablets represent the preferred class of pharmaceutical dosage forms because of their convenience in terms of patient compliances, self administration, compactness, dosage regimen, unit dosage forms and ease in manufacturing. However, an important variable in any tablet system is the rate at which the drug substance dissolves and which in turn depends on disintegration of the dosage after administration[12,13]. Such tablet fragmentation may be critical to the subsequent dissolution of the drug and to attainment of satisfactory drug bioavailability. Thus, the proper choice of disintegrants and its consistency of performance are of critical importance to the formulation development of such tablets. Various superdisintegrants like cross linked poly vinyl pyrrolidone (crospovidone), cross linked sodium carboxymethyl cellulose (AcDiSol, solutab), and sodium starch glycolate (primogel) are now frequently used in tablet formulation to ensure quick disintegration and dissolution of drug from the dosage form. Superdisintegrants may be used alone or in combination with other superdisintegrants[14]. However, the proper choice of superdisintegrants and its proportion are of significant importance in the development of tablets. Further, concentration of superdisintegrants has a major role in determining disintegration properties[15].

The major objectives of the study by considering the above aim as follows;

- To form a safe and stable dosage form.
- To improve patient compliance.

- The efficacy and safety profile of Gabapentin is well established based on extensive clinical experience in treatment of seizure.
- Reduce the risk of prescription errors
- Simplify drug manufacturing.
- Increase efficiency of drug supply management.

Plan of work:

On the basis of above aim & objectives the present study is to develop a pharmaceutically stable and robust formulation of gabapentin 800mg comparable with innovator.

- Selection of suitable superdisintegrants for immediate release tablets.
- Preformulation studies of selected superdisintegrants.
- Development of suitable analytical method for the model drug.
- Formulation of granules by adding different concentration of selected superdisintegrants by wet granulation method.
- Determination of micromere tics property of the prepared granules.
- Formulation of immediate release tablets of Gabapentin trial batches.
- Evaluation of prepared trial batches by heat and trial method.
- Optimization of the formulation batch by comparing innovator drug release profile of innovator product.
- Stability study of the optimized batch as per ICH guideline.

EXPERIMENT WORK

- **Analytical methods used:**

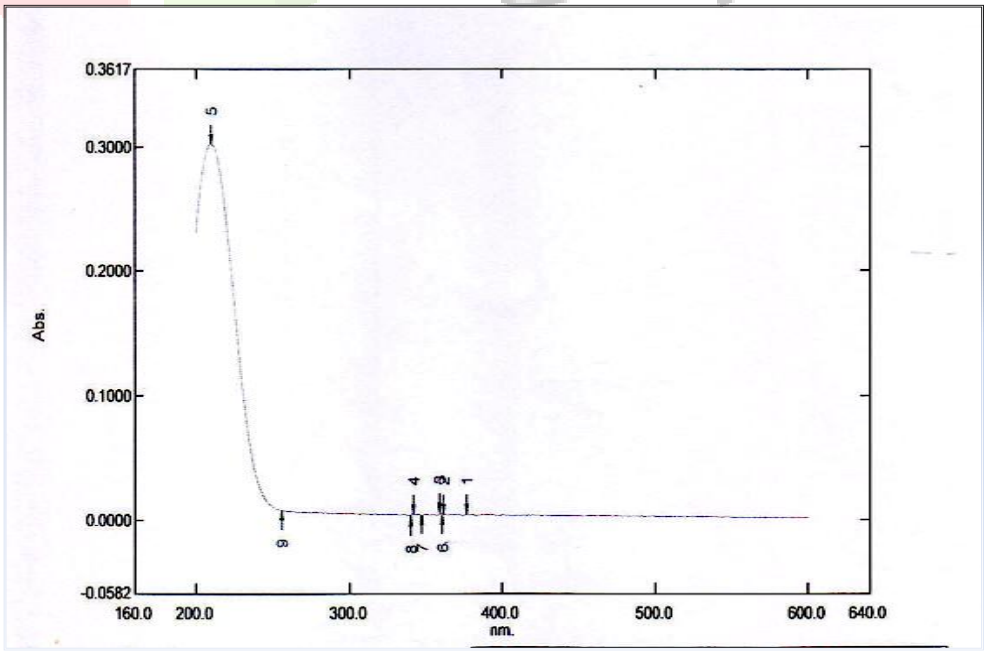

Fig. 1: Full UV-Visible spectra of Gabapentin

Construction of calibration curve for the estimation of drug:

- A standard curve was prepared in the concentration range of 500-1500 µg/ml using absorption maxima at λ_{max} 210nm. The standard stock solution was prepared by dissolving 1000mg of gabapentin in 100ml of 0.06N HCl into a 100ml volumetric flask. Add about 90ml of 0.06N HCl, sonicate to dissolve after that slowly add 0.06N HCl upto mark and mix well. From this standard stock solution pipetting out 0.5 ml, 0.75ml, 1.0ml, 1.25ml & 1.5ml of standard stock solution and transferred into a 10 ml volumetric flask and make up the volume 10ml with dissolution medium and shown the concentration of 500-1500ppm respectively. The absorbance of the resulting solutions was measured at λ_{max} 210nm keeping dissolution medium as a blank. The optical density values are recorded in table 11. Concentration versus optical density values are plotted and displayed (figure 16) in the concentration range of 500-1500 mg/ml.

Table no-1: Calibration curve data of Gabapentin

S. no	Concentration (mg/ml)	Absorbance
0	Blank	0
1	500	0.173
2	750	0.25λ4
3	1000	0.330
4	1250	0.418
5	1500	0.488

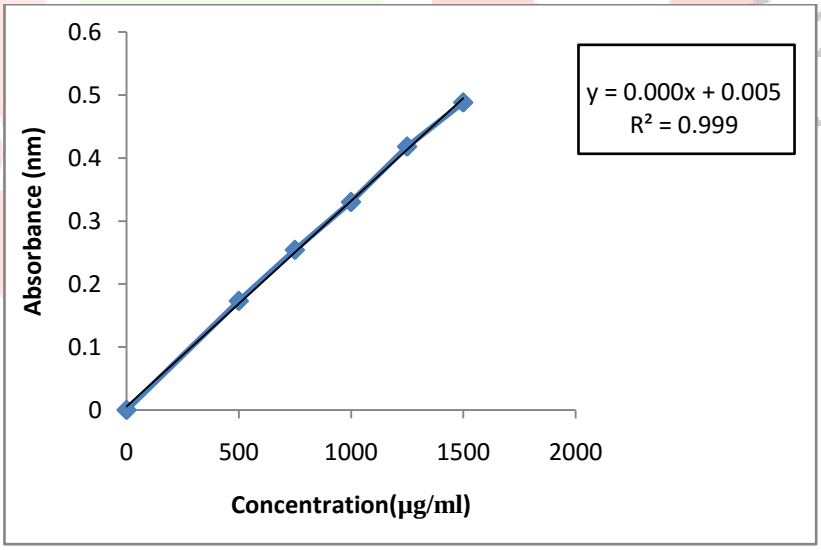

Fig. 2: Calibration curve for Gabapentin

Table no-2: List of materials used & their source

S.no.	Name of the material	Grade	Role	Supplier
1	Gabapentin USP	Amide route	API	APL
2	Corn starch USNF	Extra white Maize starch	Diluent	Rouquette

3	Crospovidone USNF	Polyplasdone XL	Disintegrant	ISP
4	Sodium starch glycolate USNF	Primogel	Disintegrant	colorcon
5	Croscarmellose sodium USNF	Ac-di-sol	Disintegrant	colorcon
6	Copovidone USNF	Kollidon VA64	Binder	BASF
7	Isopropyl alcohol USP	AR grade	Binder solution	Ranbaxy Fine Chemicals
8	Microcrystalline cellulose USNF	Ceolus KG 1000	Diluent	Asahi Kasei Chemicals Corporation
9	Microcrystalline cellulose USNF	Avicel PH 102	Diluent	FMC
10	Magnesium stearate USNF	LIGAMED MF 2V	Lubricant	Ferro Industries

Solubility:

Solubility of drug were checked out over the pH range 1-6.8. In different solvents such as water and buffers such as water, 0.1N HCl , 0.06N HCl , pH 4.5 Acetate buffer and pH 6.8 phosphate buffer. The results are seen in table-14.

Table no-3: Solubility data of gabapentin in different solvent system

Sl.no	Solvent	pH	Solubility mg/ml	Dose/Solubility ratio
1	0.1N HCl	1.2	147.95	5.41
2	0.06N HCl	1.35	137.96	5.80
3	pH 4.5 Acetate Buffer	4.5	112.95	7.08
4	Water	6.5	116.69	6.86
5	pH6.8 Phosphate Buffer	6.8	119.6	5.69

Particle size determination of the API:

Particle size determination of the API was carried out using MALVERN technique by dry method. Malvern works on the principle of laser diffraction which gives accurate results for particle size determination. The particle size of the API is depicted in table-15

Table no-16: Particle size determination of the API

Drug name	d(v,0.9)µm	d(v,0.5)µm
Gabapentin	302.58	114.91

4.4 Melting point:

Differential Scanning Calorimetry measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. Quantitative measurements of these processes have many applications in preformulation studies including purity, polymorphism, salvation, degradation, and excipients compatibility.

Method: DSC measurements were carried out using a thermal analyser-60 WS, DSC-60 (Shimadzu, japan). The samples were pure NMD, PMs and CGMs.All the samples were prepared by placing 10mg of the powder in an aluminium pan for analysis ,and each sample was heated from 30^{o}C to 300^{o}C at a rate of 10^{o}C per minute in an atmosphere of nitrogen as shown in fig-33.

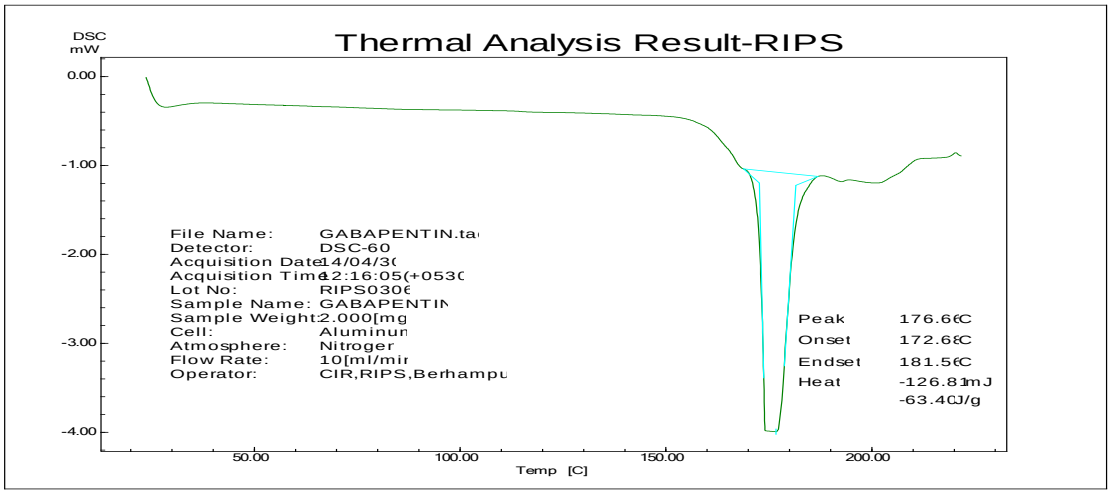

Fig. 3: Melting point of Gabapentin.

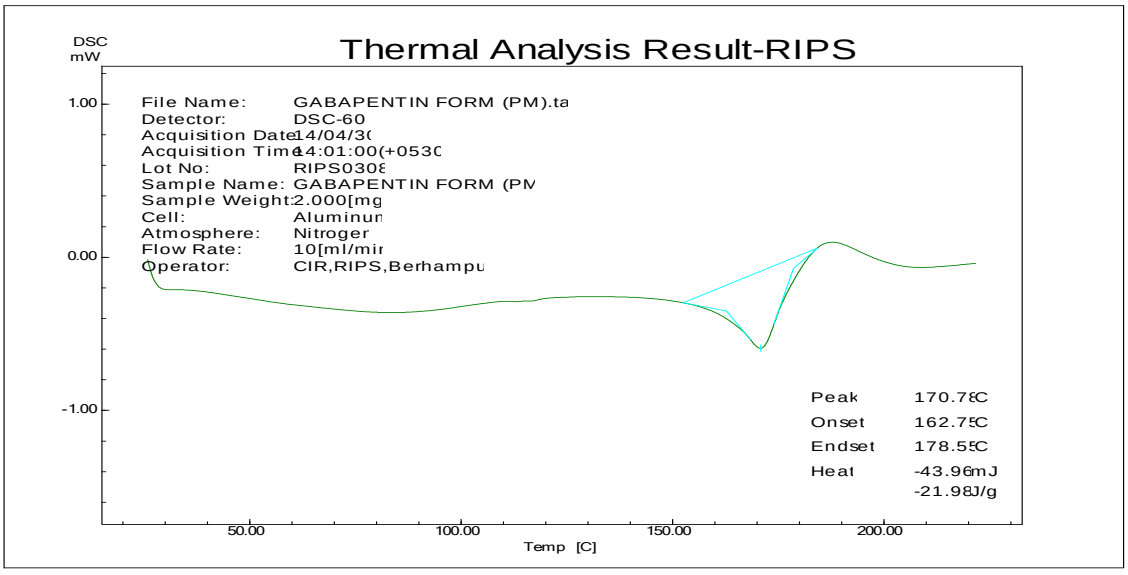

Fig. 4: DSC OF Physical mixture of drug with excipientsf **Fig. 5: DSC of crosspovidone based formulation**

Organoleptic Test:

Colour: The drug sample was viewed visually for the determination of its colour using the black and white backgrounds and then the results were compared with the official books and united state pharmacopeia. Hence the colour of the product is White.

Odour: The drug sample was smelled physically for the determination of its odour and the results were compared with the official books and united state pharmacopeia.

Micromeritics properties of the blend:

Sieve analysis:

Average size of the API's was determined using vibratory sieve shaker. 50g of API/excipients was weighed and placed on an ultrasonic sieve shaker. The test was carried out at amplitude of 50 for 10 minutes. Percentage retained on #20, #30, #40, #60, #80, #100 , #120, #140 and plate was determined and the data are shown in table no 16.

Formulation Table - 4

Name of the Ingredient	T1 (mg)	T2 (mg)	T3 (mg)	T4 (mg)	T5 (mg)	T6 (mg)	T7 (mg)	T8 (mg)	T9 (mg)
Gabapentin	300	300	300	300	300	300	300	300	300
Starch	25	20	15	25	20	15	25	20	15
Microcrystalline Cellulose	10	10	5	10	10	5	10	10	5
Crossipovidone	15	20	25						
Sodium Starch Glycollate				15	20	25			
Cross Caramellose Sodium							15	20	25
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Purified Talc	2	2	2	2	5	2	2	2	2
Total Weight(mg)	355	355	355	355	355	355	355	355	355

Trial-1:-

Table no-5: % drug release of trial-1

%age drug release							
Time (in minutes)↓/ Tablet observation→	**1**	**2**	**3**	**4**	**5**	**6**	**Average % drug release**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	89.2	89.4	89.6	89.5	89.7	89.2	89.4
15	90.8	91.8	92.2	93.6	93.1	93.5	92.5
30	94.2	94.6	94.0	94.8	94.9	95.5	94.7
45	97.8	97.9	98.2	98.6	98.8	98.9	98.4

Trial-2:-

Table no-6: % drug release of trial -2

%age drug release							
Time (in minutes)↓/ Tablet observation→	**1**	**2**	**3**	**4**	**5**	**6**	**Average %drug release**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	89.3	90.2	91.5	90.8	92.7	91.4	90.98
15	92.4	93.8	94.7	93.6	95.6	94.4	94.08
30	96.8	97.3	97.5	96.9	98.5	98.6	97.60
45	97.8	98.5	98.8	97.9	99.2	99.6	98.63

Trial-3:-

Table no-7: % drug release of trial-3

%age drug release							
Time (in minutes)↓/ Tablet observation→	**1**	**2**	**3**	**4**	**5**	**6**	**Average % drug release**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	96.0	96.0	96.1	89.6	89.6	89.4	92.8
15	97.2	97.2	97.2	94.7	94.7	94.7	96.0
30	97.3	97.1	97.2	96.3	96.2	96.2	96.7
45	97.8	97.8	97.7	96.9	96.8	96.9	97.3

Trial-4:-

Table no- 8: % drug release of trial-4

%age drug release							
Time (in minutes)↓/ Tablet observation→	**1**	**2**	**3**	**4**	**5**	**6**	**Average % drug release**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	65.4	65.5	65.5	68.9	69.1	69.1	67.3
15	86.2	86.6	86.6	89.4	90.9	90.8	88.4
30	97.8	97.8	97.6	98.1	98.1	98.1	97.9
45	97.9	97.7	97.9	98.0	97.9	98.0	97.9

Trial-5:-

Table no-9: % drug release of trial-5

%age drug release							
Time (in minutes)↓/	**1**	**2**	**3**	**4**	**5**	**6**	**Average % drug**

Tablet observation→							release
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	64.2	65.4	65.7	65.9	68.1	69.1	66.4
15	85.6	86.2	86.9	87.1	88.3	89.6	87.3
30	94.9	95.4	96.0	96.4	96.6	97.0	96.1
45	98.0	98.2	98.4	98.6	99.1	99.3	98.6

Trial-6:-

Table no-10: % drug release of trial-6

%age drug release							
Time (in minutes)↓/ Tablet observation→	**1**	**2**	**3**	**4**	**5**	**6**	**Average % drug release**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	55.0	55.5	55.5	58.3	58.9	60.2	57.2
15	75.1	75.1	75.0	78.6	79.0	79.1	77.0
30	94.8	95.2	95.3	94.7	94.7	94.6	94.9
45	96.2	96.5	96.5	95.7	95.8	95.8	96.1

Trial-7:-

Table no -11: % drug release of trial-7

%age drug release							
Time (in minutes)↓/ Tablet observation→	**1**	**2**	**3**	**4**	**5**	**6**	**Average % drug release**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	77.5	77.4	77.3	76.7	76.6	76.8	77.1
15	93.8	94.9	94.9	95.2	95.4	94.7	94.8
30	98.3	98.4	98.3	98.3	98.4	98.2	98.3
45	98.5	97.9	98.4	98.4	98.4	98.4	98.3

Trial-8:-

Table no-12: % drug release of trial-8

%age drug release							
Time (in minutes)↓/ Tablet observation→	**1**	**2**	**3**	**4**	**5**	**6**	**Average % drug release**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	64.5	64.2	64.2	64.8	64.9	64.9	64.6
15	88.6	89.2	89.4	88.9	88.8	88.6	88.9
30	98.6	98.6	98.6	99.3	99.3	99.3	98.9
45	99.0	99.0	98.9	99.0	99.3	99.1	99.1

Trial-9:-

Table no -13: % drug release of trial-9

%age drug release							
Time (in minutes)↓/ Tablet observation→	**1**	**2**	**3**	**4**	**5**	**6**	**Average % drug release**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	77.47	77.5	78.4	78.6	78.3	78.4	78.1
15	93.8	94.9	95.4	95.5	95.9	96.3	95.3
30	97.1	97.4	96.8	96.9	97.2	97.4	97.1
45	98.9	99.2	97.9	98.2	98.6	99.0	98.6

Table no-14: Comparative dissolution profile of innovators with the trail batchesT1 toT9

Time (minutes)	**Innovators**	**Trials**								
		T_1	**T_2**	**T_3**	**T_4**	**T_5**	**T_6**	**T_7**	**T_8**	**T_9**
0	0	0	0	0	0	0	0	0	0	0
10	89.01	89.4	90.98	92.8	67.3	66.4	57.2	77.1	64.6	78.1
15	94.3	92.5	94.08	96	88.4	87.3	77	94.8	88.9	95.3
30	97.5	94.7	97.6	96.7	97.9	96.1	94.9	98.3	98.9	97.1
45	98.6	98.4	98.63	97.3	97.9	98.6	96.1	98.3	99.1	98.6

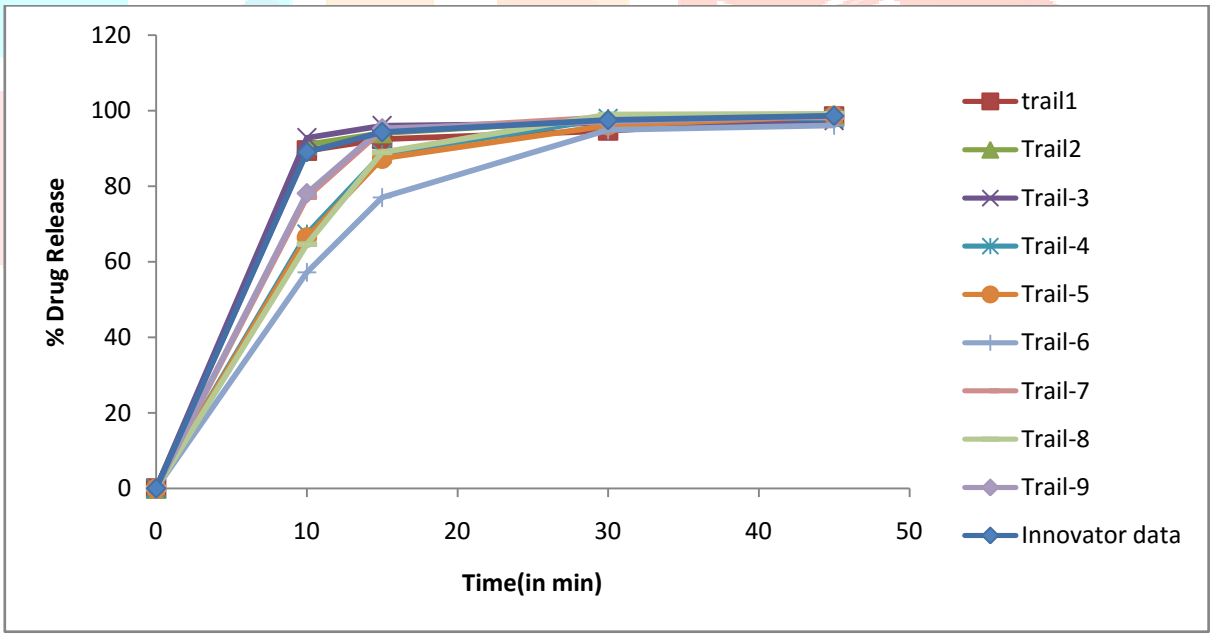

Fig. 6 : Dissolution Curves Trial 1 to Trail 9

CONCLUSION

Gabapentin is an anti-epileptic drug used in the treatment of Epilepsy. It is a water soluble drug with bioavailability of 100% and plasma half-life 5 to 7 hrs. Gabapentin tablets with various superdisintegrants were developed as oral drug delivery systems to enhance safety, efficacy of the drug molecule and to achieve better patient compliance. In the present investigation, Gabapentin tablets were formulated by wet granulation by incorporating various concentrations of superdisintegrants intra and extra granularly (IG and EG).

The following conclusions were drawn from the above study:

The compatibility study indicated that the selected drug candidate was compatible with the formulation excipients.All the formulations produce good tablets which meeting all the product specifications without any tableting problems.Among the three superdisintegrants Crospovidone is showed the better results very close to the innovator product.Trial 1 formulation (Crospovidone IG 0.5% and EG 2.8%) had exhibited uniform rheological and post compressional parameters. The *in vitro* release was matched with the innovator formulation.Trial 2 tablet with Crospovidone IG 3.3% indicated good granular blend flow and the formulated tablets showed sufficient strength with ideal hardness along with minimum friability. The same showed no weight variation of tablets during compression and the release profile was matched with the innovator.Trial 3 tablets with crospovidone EG 3.3% indicated good granular blend flow and the formulated tablets showed sufficient strength with ideal hardness along with minimum friability. The same showed no weight variation of tablets during compression and the release profile was comparable with the innovator.The results of thickness and diameter of the optimized tablets were within the limits and are in accordance with pharmacopoeial standards. The hardness was found to uniform indicating sufficient crushing strength of the tablets with friability < 1%. The drug content was found to be uniform in all the formulated tablets with low SD values.From the data, it has been concluded that the formulation (Trail 1) with crospovidone IG & EG 0.5+2.8%; (Trail 2) with crospovidone 3.3% IG; and (Trail 3) with crospovidone EG 3.3% showed uniform disintegration time which ensures faster release of the drug from the formulation.The *in vitro* studies indicated that the drug release of optimized formulations viz. Trail 1, 2, and 3 exhibited the rank order of Trail 3 < Trail 1< Trail 2 (90.73< 98.4 < 98.63).Trail 1 formulation showed sufficient rheological and tableting parameters with high release rate 98.63%. Hence it could be considered as the optimized wet granulated tablet formulation with crospovidone IG (3.3%) exhibited desired immediate drug release property.Hence, all the superdisintegrants used in the present study can be utilized in optimized/selected concentrations for the formulation of robust gabapentin tablets to enhance dissolution rate as well as improved the patient compliance.

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