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PHYSIOCHEMICAL EVALUATION OF SALT FORMS OF GABAPENTIN AND PROCESSABILITY INTO SOLID UNIT DOSAGE FORM

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ABSTRACT

Salt formation is a simple way of modifying the properties of a drug having an ionisable functional group in order to overcome some undesirable characteristics of the parent drug. An active pharmaceutical ingredient often has suboptimal physiochemical or biopharmaceutical properties that can be overcome by pairing a basic or acidic drug can be dramatically altered by salt formation. The study was design to develop different salt forms of Gabapentin which is basic in nature for its physiochemical assessment and to compare its physiochemical properties. The different acids were chose based on their pH, Solubility and category for salt formation. The prepared salt forms were characterized by pH, Solubility, Dissolution rate, Dissociation constant, Liphophilisity, DSC, XRD and FTIR. In-vitro drug release and solubility study shows increased dissolution rate and solubility as compared to the pure drug. Hydrochloride, Succinate and Tannate salt forms were used, but only Tannate salt shows improved physiochemical properties.

KEY WORDS*:* **Antiepileptic drug, Salt forms, Physiochemical properties.**

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INTRODUCTION

Salt formation is a simple way of modifying the properties of a drug having ionisable functional group in order to overcome some undesirable characteristics of the parent drug. An active pharmaceutical ingredient often has suboptimal physiochemical or biopharmaceutical properties that can be overcome by pairing a basic or acidic drug can be dramatically altered by salt formation. 50% of drugs are administered as salts converting a drug into a salt can increase its chemical stability, render the complex easier to administer and allow manipulation of agents. [1] The term pharmaceutical salt is used to refer to an ionisable drug that has been combined with a counter ion to form a neutral complex. Converting a drug into a salt through this process can increase its chemical stability, render the complex easier to administer and allow manipulation of the agent's. Salt selection is now a common standard operation performed with small ionisable molecules during drug development, and in many cases the drug salts display preferential properties as compared with the parent molecule. As a consequence, there has been a rapid increase in the number of drugs produced in salt form, so that today almost half of the clinically used drugs are salts. This, combined with the increase in generic drug production, means that many drugs are now produced in more than one salt form. In almost all cases where multiple drug salts of the same agent exist, they have been marketed as therapeutically equivalent and clinicians often treating the different salt forms identically. [2] Salt formation is an acid-base reaction involving either a proton-transfer or neutralization reaction and is therefore controlled by factors influencing such reactions. Theoretically, every compound that exhibits acid or base characteristics can participate in salt formation. Particularly important is the relative strength of the acid or base-the acidity and basicity constants of the chemical species involved. These factors determine whether formation occurs or not and are a measure of the stability of the resulting salt. The number of salt forms available to a chemist is large; surveys of patent literature show numerous new salts being synthesized annually. Various salts of the same compound often behave quite differently because of the physical, chemical, and thermodynamic properties they impart to the parent compound. For example, a salt's hydrophobicity and high crystal lattice energy can affect the dissolution rate and, ultimately, bioavailability. Ideally, it would be desirable if one could predict how a pharmaceutical agent's properties would be affected by salt formation. [3] Gabapentne is an analogue of gamma amino butyric acid (GABA) and exhibits anticonvulsant properties. This API is highly soluble but has limited and variable bioavailability, probably due to its dependence on a low-capacity amino acid transporter expressed in a limited region of the upper small intestine. Changes in solid state structure can have marked influence on the physiological absorption characteristics supporting the search for salt form as a means of improving the limited bioavailability of the drug. To alter the solubility, dissolution rate melting point and also to improve the permeability, thermal, hydrolytic and photostability as well as to reduce hygroscopicity, salt formation is one of the best methods. [4]

I. MATERIALS AND METHODS

2.1 Material

Gabapentin (Vergo company, Goa), Tannic acid (Research- lab fine chemical industry, Mumbai), Succinic acid (Poona chemical laboratory, Pune), Hydrochloric acid(Poona chemical laboratory, Pune)Micro Crystalline Cellulose (Research- lab fine chemical industry, Mumbai) were received as gift sample. Methanol, Chloroform, Distilled water, phosphate buffer pH (6.8) used throughout the study. All other chemicals and reagent were of analytical grade and were used without further purification.

2.2 salt forms Preparation

Accurately weighted quantity of gabapentin was dissolved in distilled water and resulted solution (1gm/ml) was obtained. Separately Tannic acid, Succinic acid and HCL solution was prepared (1gm/ml).These solutions were

mixed in Gabapentin solution with constant stirring on magnetic stirrer over 30-45 min. The acidic reaction yields Precipitate of salt. The salt was collected, filtered and used for further study.

2.2.1. pH dependent solubility

The pH dependent solubility of Gabapentin and its salts of tannate, Succinate and hydrochloride were determined at pH 1, 2 (HCL buffer) and pH 3, 4, 5, 6, 7, 8 (Phosphate buffer) and maintained at room temperature. Excess amount of Gabapentin and its salts were added to distilled water, solutions were sonicated for 1 hr. At room temperature, placed in a horizontal shaker at 100rpm for 24hrs. The supernant was collected, separated, filtered using U.V. Spectroscopy.

2.2.2. Determination of lipophilisity, pH and P^{Ka}

The lipophilisity, pH and P^{Ka} of Gabapentin and its salt solution were determined.

2.2.3. Spectral characterization

To investigate any possible interactions between Gabapentin and its salt forms (Tannate, Succinate and Hydrochloride) FTIR(carry 30), DSC(DSC -60, Shimadzu, Japan) were adopted.

2.2.3.1. The FTIR spectra were carried out using Agilent FTIR (carry 30) spectrophotometer. The samples were directly placed on platform and wave number selected between 4000-400 cm^{-1}.

2.2.3.2 .DSC studies were performed using (DSC -60, Shimadzu, Japan) and carried out under the following conditions: sample weight (3-10mg), Scanning rate 10^{0c}/min and temperature range (25-300^{0c}). Indium was used as standard.

2.2.3.3. UV analysis of drug and prepared salts were investigated with the spectrophotometric assay of Gabapentin as follows. A specified concentration of gabapentin in phosphate buffer solution having pH 7.2 was scanned at 200-400nm to determine the wavelength of maximum drug absorption. UV spectrophotometric scanning of Gabapentin solution and salt solution in pH 7.2 PBS was also investigated at the same wavelength interval to determine whether any interference with the drug assay may take place.

2.2.3.4. PXRD studies were performed using (D-max X-ray flows spectrophotometer) with cu ka wire as a source of radiation and carried out under following conditions. Current 182Mv, scanning rate 2^0/min and Φ range of 5-70^{0c}.

2.2.4.In-vitro dissolution studies for salt forms of Gabapentin

Performed using USP dissolution apparatus I at 100 rpm.1gm of Gabapentin salt forms were placed in a basket which was then placed in 900 ml of water maintained at 37^0c ± 0.5 ^{0}c. 5ml samples were withdrawn predetermined time points of 10, 20, 30, 40, 50, 60, 70,80and 90 min. The 5 ml sample withdrawn was replaced by the fresh phosphate buffer solution (pH 6.8)and maintained at 37 ± 0.5°C. At certain intervals samples from dissolution medium were withdrawn and filtered, and concentrations of salt forms were determined spectrophotometrically at 232 nm.

2.3. Formulation of Gabapentin conventional tablet

2.3.1. Preparation of mixture blend:

First Aerosil and sodium alginate with drug mixed well by dry mixing .The microcrystalline cellulose and Magnesium stearate adding to their mixing thoroughly with first mixture.

2.3.2. Preparation of Gabapentin tannate tablet

According to Table raw materials of each formulation were weighed and were mixed for 15 min. After preparation of primary powder mixtures including Aerosil, sodium alginate and Magnesium stearate passed through appropriate mesh and were added to the powders and this was mixed together for 5 min. Finally the selective lubricants PVPK-30was added and again mixed for about 2-5 min with above material. Tablets were made in hand punch machine by using 13 mm punches The tablet 300 mg in bases.. The Gabapentin tannate tablet prepared by direct compression method according to formula in given table 7.10 a total number of nine formulations (F1 to F9) of Gabapentin tannate tablet were prepared. Before tablet preparation the mixture blend of the formulation was subjected to precompression studies like angle of repose, bulk density,

tapped density, compressibility index, hausners ratio.

2.4. Precompression characterization of selected salt

2.4.1. Angle of repose

The angle of repose of powder blend was determined by the funnel method. The 10 gm of accurately weighed powder blends were taken in funnel. The height of the funnel was adjusted 2 cm above the tip of the funnel which just touches the heap of the powder blend. The powder blends were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. The mean ± standard deviation values of angle of repose were calculated.

2.4.2. Bulk density

Accurately weighed 10 gm of powder blend from each formulation was taken in a measuring cylinder and the initial volume of the powder blend in the measuring cylinder was noted .This was calculated by using the following formula. The mean ± standard deviation values of bulk density were calculated.

2.4.3. Tapped density

The volume was measured by tapping the powder blend for 100 times. Tapped density was calculated by using the following formula. The mean ± standard deviation values of tapped density were calculated.

2.4.4. Compressibility index and Hausners ratio

The compressibility index of the powder blend was determined by Carr's compressibility index and the Hausners ratio.

2.5. Post compression characterization of selected salt

2.5.1. Hardness

Hardness of the tablet of each formulation was determined using Pfizer hardness tester. Three tablets from each formulation batch were tested randomly and the average reading was noted. The mean ± standard deviation values of hardness were calculated.

2.5.2. Thickness

The thickness of the tablets was measured with a screw gauge micrometer that had a 0 to 25 mm scale and was capable of differentiating up to 0.01 mm. The tablet thickness is expressed as averages of 5 measurements made at 5 different points between the 2 surfaces of the compact. The mean ± standard deviation values of thickness were calculated.

2.5.3. Disintegration time

Nine hundred milliliters of water maintained at 37˚C. DT was determined at the point at which the tablet disintegrated and passed through the screen of the sinker completely (opening of mesh of the sinker: 3–3.5 mm in height and 3.5–4 mm in width). The mean ± standard deviation values of DT were calculated.

2.5.4. Friability

Roche friabiliator was used for the friability. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 4 inches with each revolution. Pre-weighed 20 tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. The mean ± standard deviation values of % fraibility were calculated.

2.5.5. % drug release

The dissolution test was performed using 900 ml of phosphate buffeer (pH=6.8), at 37 ± 0.5°C and 50 rpm. A sample (1ml) of the solution was withdrawn from the dissolution vessel at 10, 20, 30, 40, 50, 60,70,80 and 90 min time intervals. The samples were replaced with fresh dissolution medium of the same quantity. The samples were filtered through a whatman filter. Absorbance of these solutions was measured at 232 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve. The mean ± standard deviation values of dissolution were calculated.

II. RESULTS AND DISCUSSION

3.1. Characterization of Drug

The received samples were identified by various tests.

3.1.1. UV spectra of Gabapentin

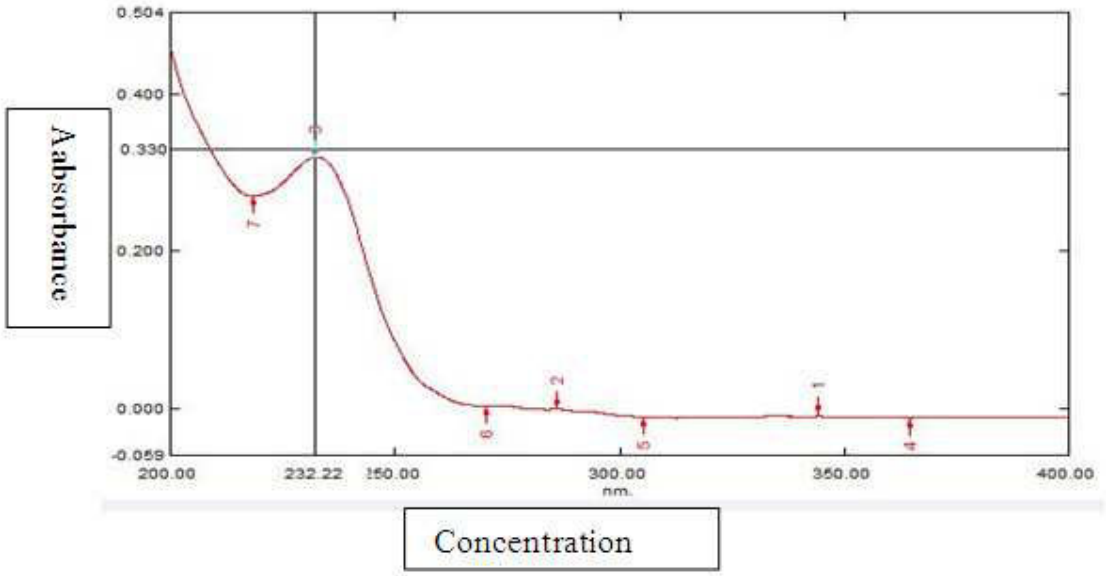


Figure no.1
UV spectra of Gabapentin

The maximum absorption value of pure drug, Gabapentin was found at232.0 nm wavelength. Therefore232.0 was recorded as λ max of the pure drug Gabapentin. The observed λ max value of drug was found to be similar as given in literature. Hence the drug was considered to be pure.

3.1.2. pH dependent solubility

pH	Solubility(mg/ml)			
	Pure Gabapentin	Gabapentin succinate salt	Gabapentin hydrochloride salt	Gabapentin tannate salt
1	1.40	0.79	0.89	1.90
2	6.25	0.85	0.88	1.40
3	5.14	0.88	1.39	1.15
4	3.16	1.09	1.29	1.90
5	3.96	2.47	2.98	4.32
6	2.95	4.02	5.040	6.35
7	1.50	0.89	1.5	1.71
8	1.39	4.10	5.05	7.06
Water	4.40	4.54	5.51	9.88

Table no.1
pH dependent solubility

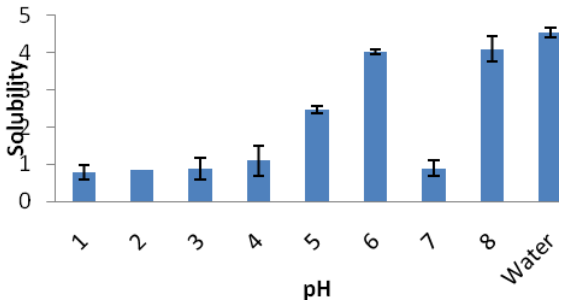


Figure no.2
pH dependent solubility of Gabapentin succinate salt

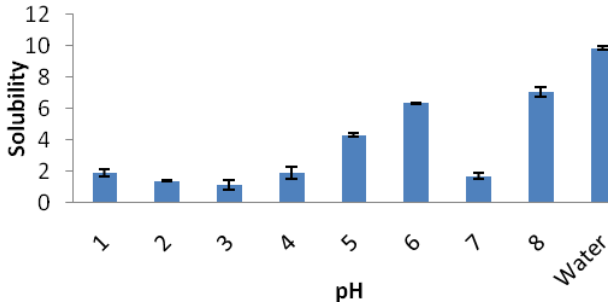


Figure no.3
pH dependent solubility of Gabapentin hydrochloride salt

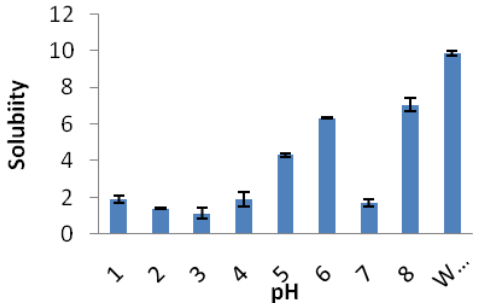


Figure no.4
pH dependent solubility of Gabapentin tannate salt

The pure drug Gabapentin which is basic in nature, having solubility more in acidic pH. In pH 2and 3 it has solubility 6.25 and 5.14mg/ml which more as compared to the basic pH as it is basic in nature it dissociate more in acidic pH. When the drug was converted to the salt form its salt forms having solubility more in basic pH as its pH was changed to the acidic pH and from this salt forms the Gabapentin tannate salt having greater solubility in basic pH that is in pH 6 and 8 it having 6.35 and 7.06 mg/ml where as the succinate and hydrochloride salt having low solubility as compared to the tannate salt.

3.1.3. Spectral analysis
3.1.3.1. FTIR analysis

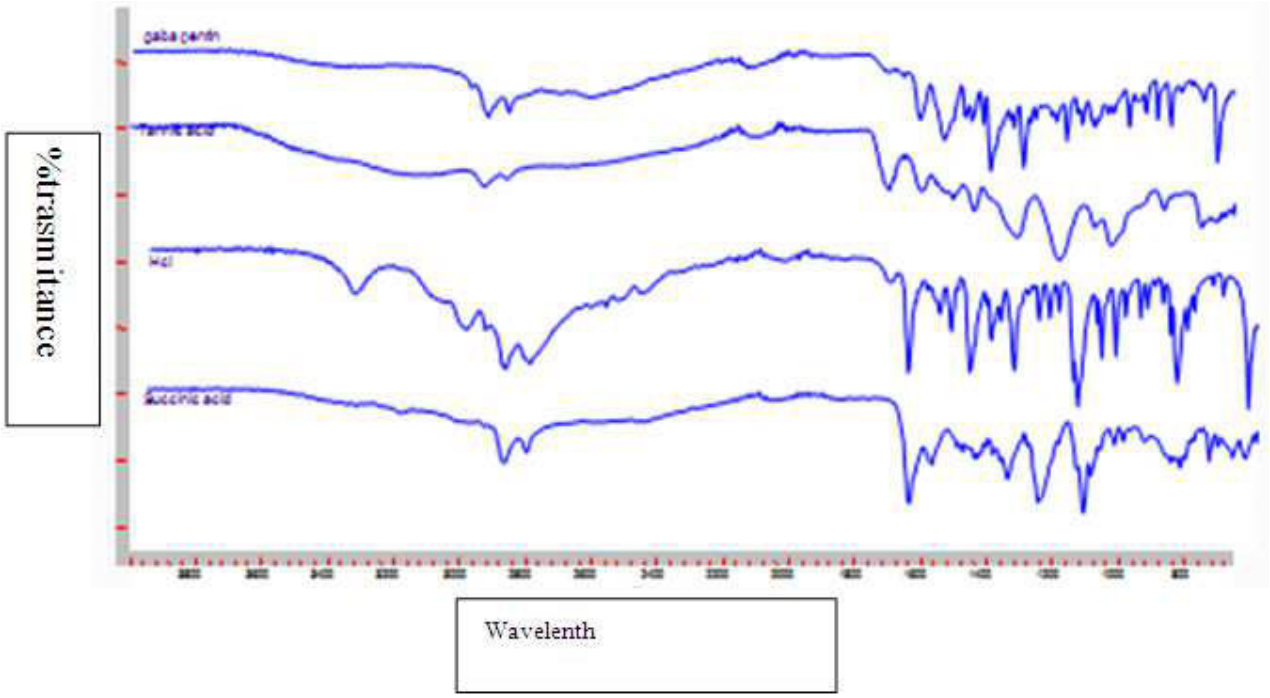


Figure no.5
FTIR spectra of Gabapentin and salt form

Infrared spectroscopy has established itself as a valuable tool for the determination of organic and to lesser extent inorganic structure. Utilization of infrared data in conjunction with other physical measurements such as those obtained from nuclear magnetic resonance and mass spectroscopy, has elucidated many facts about the structure and properties of organic compound. Various bands will be present in IR spectrum which will correspond to the characteristics functional group and bonds present in a chemical substance. Pure drug Gabapentin and was subjected for IR spectroscopic analysis, to ascertain whether there is any impurity was found in drug. The IR spectra obtained was shown in Figure The IR spectra of drug functional peaks at 1600.22, 1536.32 and 1657.92cm^{-1}.This peaks indicate that the drug was having the similar functional group**.** All classes of compound that is alcohols, esters and lactones shows characteristics absorptions (strong bands) in the region due to C-O stretching .Ester shows two strong bands at 1350-1260cm^{-1}.The IR of Gabapentin tannate salt was shown absorption at 1316 cm^{-1} which was indicate that there was formation of ester. The spectrum show the presence of strong amid, The N-H stretching (associated at 3238.62cm^{-1}) and NH deformation and carbonic stretching (ester) exhibited at 1701cm^{-1} .The O-H deformation of Gabapentin at 1316cm^{-1} .The other peaks that is C-H stretching (aromatic), C-H (aliphatic) stretching shows the sharp peaks around 2859 to 2927cm. The frequency shifts from the normal position of absorption occur because of electronic effects which include inductive effect, mesomeric effect. Under the influence of these effects, the force constant or the bond strength changes and its absorption frequency shift from the normal value. The synthesis of Gabapentin hydrochloride salt was carried out in the ratio 1:1 was confirmed by IR spectroscopy. The spectrum shows the presence of symmetrical and unsymmetrical peaks at the 1711cm and 1559cm which indicate the presence of strong C=O group. The peak at 1524.72cm indicates the presence of aromatic ring and at the 1391.64cm indicates presence of O-H stretching. The spectrum show the presence of strong, oxime linkange The N-H stretching

(associated at 3238.62cm^{-1}) and NH deformation and carbonic streching (ester) exhibited at 1701cm^{-1} .The O-H deformation of Gabapentin at 1316cm^{-1} .The other peaks that is C-H stretching (aromatic), C-H (aliphatic) stretching shows the sharp peaks around 2859 to 2927cm.

3.1.3.2. DSC analysis

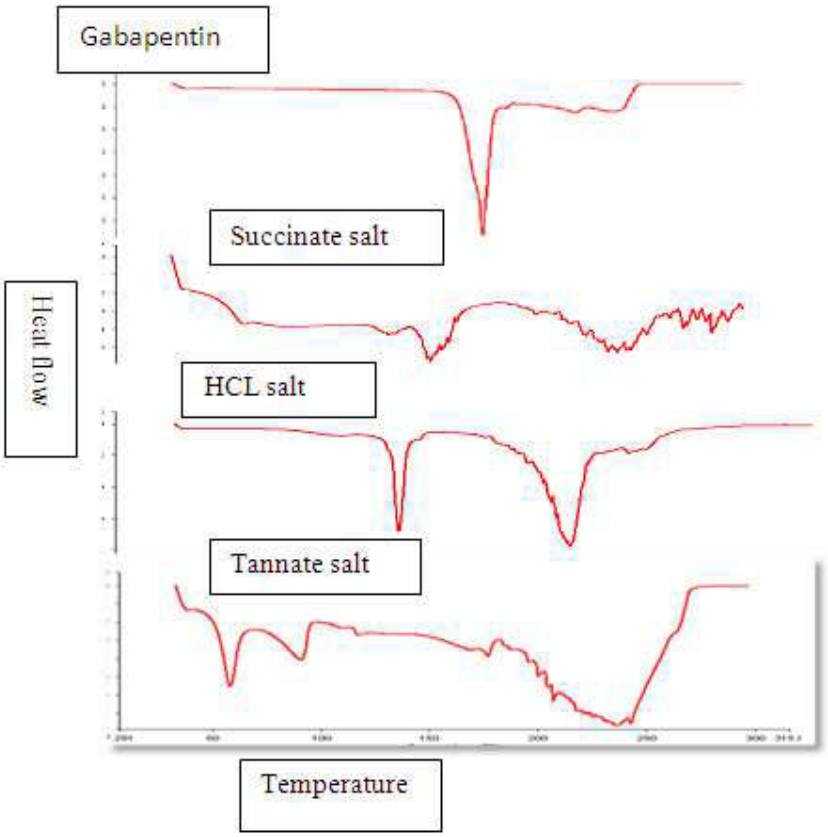


Figure no.6
DSC analysis of Gabapentin and its salt form

DSC consists of record of the difference in sample and reference temperature. Generally sharp endothermic peaks give idea about changes in crystanility whereas broad endothermic signify dehydration reaction .In most of cases physical changes give rise to endothermic peak curve whereas chemical reaction gives exothermic peak. Differential scanning calorimetry (DSC) can be used to investigate and predict physicochemical interaction between components in a formulation thus helps in selecting suitable chemically compatible excipients. Any interaction would be indicated in the thermogram of a mixture by the appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of the components. Any polymorphic change in the drug causes changes in the melting point, bioavailability and release kinetics.The Gabapentin showed the sharp melting endothermic peak at 164^{0}c on other hand the Gabapentin succinate salt showed the melting endothermic peak at 130 and also shows the broad exothermic peak at 150^{0}c which indicate that there is change in crystanility into the drug when converted to the salt form. The salt form showed decrease in the melting point due to the decrease in the lattice energy due to converted to salt form. Physical changes give rise to endothermic peak curve whereas chemical reaction gives exothermic peak. In that case there was both endothermic and exothermic peak occurs which indicate that there was physical as well as chemical changes occurs. The Gabapentin

showed the sharp melting endothermic peak at 164 on other hand the Gabapentin tannate salt showed the melting endothermic peak at 90 and also shows the broad exothermic peak at which indicate that there is change in crystanility into the drug when converted to the salt form. The salt form showed decrease in the melting point due to the decrease in the lattice energy due to converted to salt form.The solubility of a compound depends basically upon the physical and chemical properties of solute that is a lower melting point for a compound within a series reflects a decrease a lattice energy which suggest a higher solubility as compared to the drug and two other salts the Gabapentin tannate salt having low malting point. As melting point can easily determine by DSC it means that this technique can be used as direct check of purity of the compound. Physical changes give rise to endothermic peak curve whereas chemical reaction gives exothermic peak. In that case there was both endothermic and exothermic peak occurs which indicate that there was physical as well as chemical changes occurs due to the formation of salt forms.

3.1.3.3. XRD analysis

This method determines the degree of crystanality of the compound. The non crystalline portion simply scatters the X-ray beam to give continuous background, while the crystalline portion causes diffraction lines that are not continuous. As compared to the drug and two other salts Gabapentin tannate salt shows the diffraction pattern at low intensity which indicate that it was there was decrease in the crystanality of salt as compared to the pure drug.

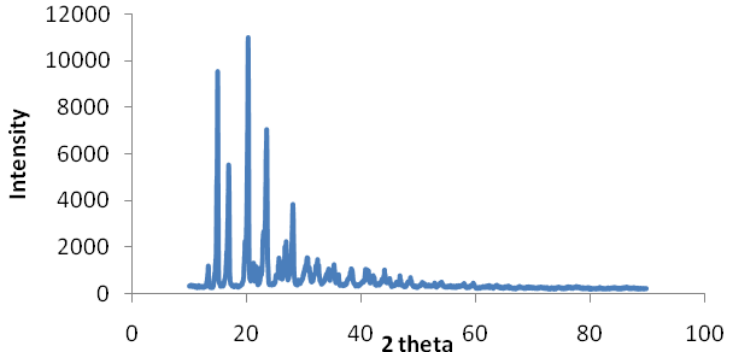


Figure no.7
Powder X-ray diffraction of Gabapentin

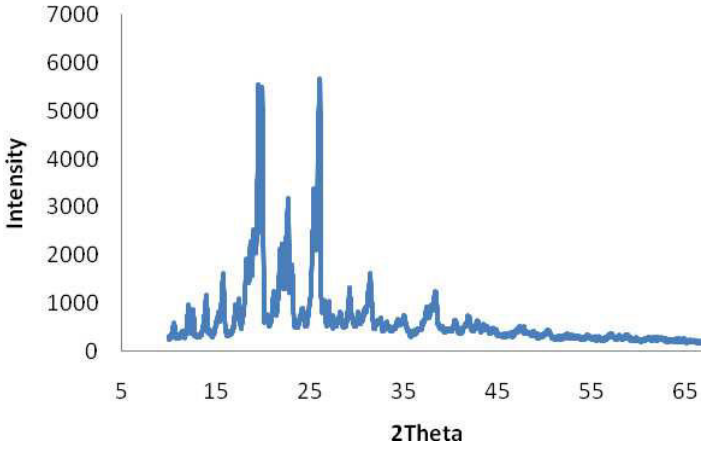


Figure no.8
Powder X-ray diffraction of Gabapentin succinate salt

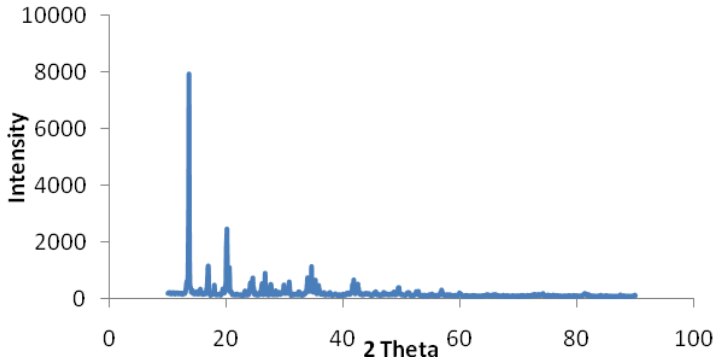


Figure no.9
Powder X-ray diffraction of Gabapentin hydrochloride salt

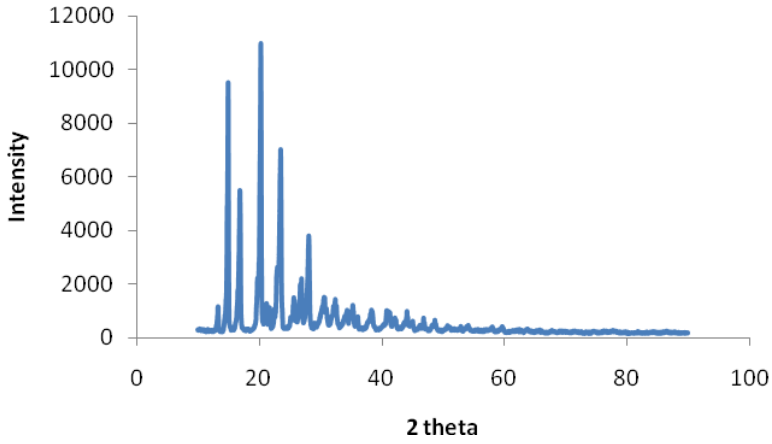


Figure no.1o
Powder X-ray diffraction of Gabapentin tannate salt

The drug was shows the diffraction pattern at 2theta values also the Succinate, hydrochloric and tannate salt forms of Gabapentin shows the diffraction pattern at different 2theta values but the salt forms shows the diffraction at low intensities as compared to the drug which indicates that the crystanality of salt forms was slightly decreased. The Tannate salt shows diffraction at lowest value as compared to their two salts.

3.1.4. Dissolution study

Time (min)	% drug release			
	Gabapentin	Gabapentin succinate salt	Gabapentin hydrochloride salt	Gabapentin tannate salt
10	51.64±0.41	69.99±0.005	72.01±0.56	78.07±0.41
20	51.84±0.08	70.34±0.01	72.07±0.01	78.89±0.64
30	52.27±0.011	70.60±4.65	72.36±0.01	80.46±0.19
40	52.43±0.2	72.60±0.11	72.62±0.21	81.36±0.08
50	53.48±0.35	73.65±0.02	73.02±0.31	81.73±0.098
60	54.09±0.5	74.25±0.02	73.9±0.46	83.99±0.005
70	57.48±0.08	74.74±0.14	74.75±0.14	84.32±0.16
80	59.17±0.35	74.89±0.005	75.58±0.011	85.04±0.46
90	61.50±0.017	76.37±0.017	77.52±0.04	85.48.011

Table no 2
Dissolution study of Gabapentin and its salt form

Dissolution study is alternative for in-vivo bioavailability study it is not possible at every time to do bioavailability study in animal because it is time consuming ,tedious and expensive so in-vitro dissolution study performed and found that the bioavailability of drug. The bioavailability of gabapentin was found to be 60% while the bioavailability of their salt forms that is Gabapentin succinate, Gabapentin tannate and Gabapentin hydrochloride 76.37%, 85.48and 77.52% respectively. In comparison to the drug and hydrochloride and succinate Gabapentin tannate salt having high dissolution rate. From saturation solubility data it is found that Gabapentin having low solubility in basic pH but when it converted to salt form it having high solubility in basic pH. Gabapentin tannate salt having high solubility in basic pH as compared to the succinate and hydrochloride salt. In salt formation dissolution improvement was might be because of decrease in the crystanality. From dissolution profile of salt forms Gabapentin tannate salt found that to achieve 85.48% drug release in 90 min and Succinate and hydrochloride salt having 76.37% and 77.52% drug release from this result it was concluded that tannate salt showed better drug release.

3.1.5. Release kinetics study of salt forms of Gabapentin

Drug/Salt forms	Zero order kinetics	First order kinetics	Higuchi model	Hixon Crowell
	Regression value			
Gabapentin tannate salt	0.98	0.90	0.96	0.99
Gabapentin hydrochloride salt	0.96	0.90	0.96	0.99
Gabapentin succinate salt	0.98	0.90	0.96	0.99

Table no. 3
Release kinetics study of salt forms of Gabapentin

The above studies follows regression values of First order, Zero order, Higuchi and Hixon Crowell models .From the above results the Hixon Crowell model was found to be best fit model for Gabapentin tannate, succinate and hydrochloride salt.

3.1.6. Comparative physiological evaluation of Gabapentin salt forms

Sr.no	Test	Gabapentin	Salt with tannic acid	Salt with succinic acid	Salt with HCL
1	Nature	Colour-White State-solid (Crystalline)	Colour-Brown State-solid (Crystalline)	Colour-White State-solid (Crystalline)	Colour-White State-solid (Crystalline)
2	pH	6.57	4.96	5.30	5.80
3	Melting point	164°C	90°C	150°C	130°C
4	Water solubility (mg/ml)	4	9.88	4.54	4.40
5	%drug release	60%	85.48	76.37	74.74
6	Dissociation constant	4.53	8.11	7.98	8.2
7	Partition coefficient	-1.9	1.34	0.58	o.98

Table no. 4
Comparative physiological evaluation of Gabapentin salt forms

After the comparison of all physiochemical properties of Succinate, Hydrochloride and Tannate salt of Gabapentin it was clear that the Gabapentin tannate salt give the optimized result that is it has high solubility, high dissolution rate and also the partition coefficient and dissociation constant as compared to the drug and two other salt forms .In case of weak acid which having dissociation constant value greater than 8 it was unionized at all pH and well absorbed from GIT track. In case of log P value according to the Lipnsiki rule 5 a drug having log P value greater than 5 would not have

good absorption property so will not be good choice as drug and in case of CNS acting drug drug having log P value less than 5 easily absorbed in BBB and if the value is less than 0 it will move towards hydrophilic compartment like blood serum.

3.2. Formulation table

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Gabapentin tannate salt	130	130	130	130	130	130	130	130	130
Aerosil	10	10	10	10	10	10	10	10	10
Sodium alginate	45	40	40	4o	47	35	45	32.92	35
MCC	122.5	122.5	122.5	122.5	122.5	122.5	122.5	122.5	122.5
PVPK-30	15	16.55	5.94	11.25	11.25	15	7.5	11.25	7.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight of tablet	500	500	500	500	500	500	500	500	500

3.2.1. Evaluation of Physical Properties of Tablet Blend

Formulation	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr`s Index (%)	Hausner`s Ratio
F1	29.05 ±0.12	0.47±0.0.5	0.53 ±0.01	11.79±0.10	1.13 ±0.05
F2	28.39±0.005	0.49± 0.01	0.56± 0.01	11.50 ±0.2	1.13 ±0.05
F3	27.75 ±0.01	O.53 ±0.1	0.61 ±0.01	12.94 ±0.2	1.14±0.0.1
F4	29.74 ±0.01	O.53± 0.2	0.59± 0.03	10.16±0.01	1.11±0.015
F5	30.46± 0.02	0.50± 0.35	0.56±0.02	11.50±0.35	1.13 ±0.05
F6	28.39 ±0.1	0.57 ±0.4	0.62 ±0.31	7.58 ±0.12	1.08 ±0.15
F7	31.21 ±0.02	0.49 ±0.6	O.56 ±0.35	12.44±0.15	1.13 ±0.1
F8	29.74±0.01	0.51 ±0.35	0.57 ±0.02	10.56±0.01	1.11 ±0.15
F9	30 ±0.12	O.57 ±0.5	0.62± 0.1	7.58 ±0.12	1.08± 0.35

Table no.5
Evaluation of Physical Properties of Tablet Blend

3.2.2. Physical Properties of Tablets

F.C.	Hardness(N)	Thickness (mm)	Disintegration time (Sec)	Friability (%)	%drug release
1	89 ±1	3.48± 0.01	150 ±3.77	0.74 ±0.1	76.23±0.25
2	70 ±0.05	3.46±0.1	155 ±2.70	0.45 ±0.2	74.12 ±0.1
3	84 ±0.12	3.44±0.02	150 ±1.50	0.67 ±0.01	82.48±0.35
4	85 ±0.05	3.48±0.035	152 ±2.25	0.35 ±0.05	78.45±0.28
5	68 ±0.13	3.43±0.15	158 ±3.14	0.55 ±0.35	79.11±0.15
6	89 ±0.16	3.48±0.02	145 ±2.15	0.54 ±0.2	75.34±0.05
7	79 ±0.15	3.47±0.2	148 ±1.52	0..63± 0.1	83.23±0.35
8	*85* ±0.4	3.46 ±0.03	142 ±3.77	0.72 ±0.035	*85.65*±0.1
9	86 ±0.35	3.48±0.02	145 ±2.25	0.58 ±0.5	83.48±0.45

Table no.6
Physical Properties of Tablets

3.3. Optimization Study

Evaluation of Gabapentin tannate tablet

Factorial design was used to optimize the concentration of Sodium alginate and PVPK-30. Gabapentin tannate tablet were prepared subsequent a factorial design, the composition as follows

3.3.1. Formula for Gabapentin tannate tablet : (Optimized Batch)

Sr. No	Ingredients	Quantity mg
1	Gabapentin tannate salt	130
2	Aerosil	10
3	Sodium alginate	32.92
4	MCC	122.5
5	PVPK-30	11.25
6	Magnesium stearate	1.5
7	Total weight of tablet	500

Table no.7
Formula for Gabapentin tannate tablet : (Optimized Batch)

3.3.1.1. Precompression properties

The value of angle of repose was found to be below 30 which indicate good flow property. The bulk density and tapped density value was found to be less than one that also indicate the good flow properties of tablet blend. Similarly the percentage compressibility (Carrs Index) value was less than 16% and hausner ratio shows normal level.

Sr. No	Precompression Properties	
1	Angle of repose (Φ)	29.74
2	Bulk Density (gm/cm^3)	0.57
3	Tapped Density (gm/cm^3)	0.62
4	Carrs Index	10.56
5	Hausners Ratio	1.11

Table no. 8
Precompression properties

3.3.1.2. Evaluation of Gabapentin tannate tablet

The physical evaluation of effervescent tablet was given in table 7.22. The hardness value of tablet formulation was found to be85N.The tablet formulation friability seen by the below one % that also complies the test as per the USP. The thickness of prepared effervescent tablet was found to be 3.46mm. The result was found within pharmacopoeia limit.

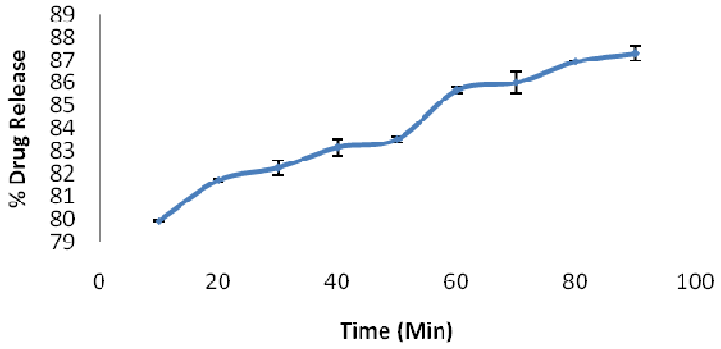
Physical evaluation of tablet

Sr. No	Physical Evaluation of Tablet	Result
1	Hardness (N)	85
2	Thickness (mm)	3.46
3	Friability (%)	0.72
4	Disintegration time(Sec)	142

Table no. 9
Physical evaluation of for Gabapentin tannate tablet

Drug release profile of tablet formulation

Time in (minute)	% Drug release
10	79.92±0.04
20	81.72±0.07
30	82.26±0.31
40	83.16±0.36
50	83.52±0.14
60	85.68±0.12
70	86.02±0.48
80	86.94±0.03
90	87.3±0.32



Drug release profile of formulation

III.CONCLUSION

A number of methodology can be adopted to improve solubility of drug and further to improve its bioavailability .These techniques can be chosen on the basis of certain aspects such as properties of drug, nature of excipients and nature of intended dosage forms. salt formation is a simple way of modifying the properties of a drug having ionisable functional group in order to overcome some undesirable characteristics of the parent drug .An active pharmaceutical ingredient often has suboptimal physiochemical or biopharmaceutical properties that can be overcome by pairing a basic or acidic drug can be dramatically altered by salt formation.50% of drugs are administered as salts converting a drug into a salt can increase its chemical stability render the complex easier to administered and allow manipulation of agents. For the present work Gabapentin was selected as model drug candidate. A preformulation study was carried out during the early stage of this work it has found that Gabapentin was having maximum absorption at 232nm. FTIR technique is based upon the simple fact that a chemical substance shows marked selective absorption in the infrared region. Various bands will be present in IR absorption spectrum which will corresponds to the characteristics functional groups and a bonds present in chemical substance. All classes of compound that is alcohols, esters and lactones shows characteristics absorptions (strong bands) in the region due to C-O stretching .Ester shows two strong bands at 1350-1260cm^{-1}.The IR of Gabapentin tannate salt was shown absorption at 1316 cm^{-1} which was indicate that there was formation of ester. The spectrum shows the presence of strong amid, The N-H stretching (associated at 3238.62cm^{-1}) and NH deformation and carbonic stretching (ester) exhibited at 1701cm^{-1} .The O-H deformation of Gabapentin at 1316cm^{-1} .The other peaks that is C-H stretching (aromatic), C-H (aliphatic) stretching shows the sharp peaks around 2859 to 2927cm. DSC consists of record of the difference in sample and reference temperature. Generally sharp endothermic peaks give idea about changes in crystanility whereas broad endothermic signify dehydration reaction .In most of cases physical changes give rise to endothermic peak curve whereas chemical reaction gives exothermic peak. The solubility of a compound depends basically upon the physical and chemical properties of solute that is a lower melting point for a compound within a series reflects a decrease a lattice energy which suggest a higher solubility as compared to the drug and two other salts the Gabapentin tannate salt having low malting point. As melting point can easily determine by DSC it means that this technique can be used as direct check of purity of the compound. Physical changes give rise to endothermic peak curve whereas chemical reaction gives exothermic peak. In that case there was both endothermic and exothermic peak occurs which indicate that there was physical as well as chemical changes occurs due to the formation of salt forms. X-diffraction method determines the degree of crystanality of the compound. The non crystalline portion

simply scatters the X-ray beam to give continuous background, while the crystalline portion causes diffraction lines that are not continuous. as compared to the drug and two other salts Gabapentin tannate salt shows the diffraction pattern at low intensity which indicate that it was there was decrease in the crystanality of salt as compared to the pure drug. In case of weak acid which having dissociation constant value greater than 8 it was unionized at all pH and well absorbed from GIT track. In case of log P value according to the Lipnsiki rule 5 a drug having log P value greater than 5 would not have good absorption property so will not be good choice as drug and in case of CNS acting drug drug having log P value less than 5 easily absorbed in BBB and if the value is less than 0 it will move towards hydrophilic compartment like blood serum.The Gabapentin salt forms having log P value less than 5 while the Gabapentin having less than zero which concluded that the salt forms having better partition coefficient value than the Gabapentin. Dissolution study is alternative for in-vivo bioavailability study it is not possible at every time to do bioavailability study in animal because it is time consuming ,tedious and expensive so in-vitro dissolution study performed and found that the bioavailability of drug. The bioavailability of gabapentin was found to be 60% while the bioavailability of their salt forms that is Gabapentin succinate, Gabapentin tannate and Gabapentin hydrochloride 76.37%, 85.48and 77.52% respectively. In comparison to the drug and hydrochloride and succinate Gabapentin tannate salt having high dissolution rate. The salt forms were formulated by precipitation method by using different acids and ths different acids were selected based on their pH, solubility and there category .After comparative study of the all salt forms of the Gabapentin salt form with tannic acid gives best result that is solubility, Dissociation constant, Partition coefficient and Dissolution rate. Upon processability into the solid unit dosage form there was no change into the Dissolution rate. The two variables were studied at 3 level it give nine different formulations were developed and evaluated .The salt formed with tannic acid showed best result among other two salts. From the above discussion it was concluded that formulation of salt form found to be effective way for the assessment of physiochemical properties.

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