ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in
Ramu Samineni et al /J. Pharm. Sci. & Res. Vol. 12(5), 2020, 639-648

Effect of Coformers on Novel Co-Crystals of Gabapentin: An *In Vivo* Approach

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Abstract:

Background: Poor aqueous solubility and low oral bioavailability of an active pharmaceutical ingredient are the major constraints during the development of new product

Aim: The aim of the current work is to formulate and evaluate the Gabapentin co-crystals with various co formers like benzoic acid, salicylic acid and Tartaric acid. **Method:** Novel co-crystals in current study was prepared by using solvent drop method, co-grinding method and solvent evaporation method in stichiomentric ratio of 1:1. Co-crystals were characterized by standard calibration curve, FTIR, PXRD, flow properties, intrinsic solubility, dissolution rate and *in vivo* study.

Results: The prepared multicomponent co-crystal formulations evaluated for saturation solubility analysis in case of pure Gabapentin showed 5.99 (mg/ml), GBP-TA CF showed high solubility values 13.52 folds solubility increases. The new crystalline forms are characterized by PXRD and NMR.

Conclusion: The drug release profile high in GBP-BA CF (98.3%) at the end of 360th minute while compared to other formulations. GBP-TA CF showed high regression value (0.998) and diffusion release exponent showed 0.792 so this formulation was selected as optimized formulation following non Fickian release mechanism, and selected for in vivo study. The percentage protection high in GBP-TA co crystal formulation dose of 10 mg/kg compared to other doses. The dose size decreases and percentage protection increasing showing greater control of toxicity.

Keywords: Co-crystal, Intrinsic Solubility, In vitro dissolution, Maximum Electroshock seizure.

INTRODUCTION

Gabapentin (GBP) (1-(amino methyl) cyclohexaneacetic acid), is an antiepileptic drug which is a structural analogue of neurotransmitter γ-amino butyric acid (GABA) represented in figure 1. Gabapentin (brand name Neurontin) is a medication originally developed for the treatment of epilepsy. Presently Gabapentin is widely used to relieve pain, especially neuropathic pain. Gabapentin is well tolerated in most patients, has a relatively mild side-effect profile, and passes through the body un metabolized [1]. Gabapentin is freely soluble in water at 25 ^{0}C and slightly soluble in ethanol

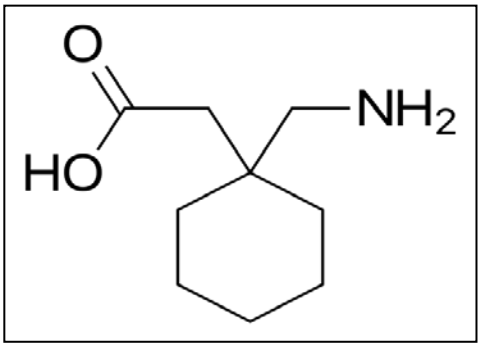

Fig. 1 Chemical structure of Gabapentin

Gabapentin showing rapid absorption rate. Drug bioavailability appears to decrease as the dose increases but is reported to be 80% for a dose of 50 mg/kg/day, about 34% of Gabapentin is metabolized by the liver. The terminal half-life of Gabapentin is 4.5 to 6.5 hours. Drug readily crosses the blood–brain barrier and enters the central nervous system [2]

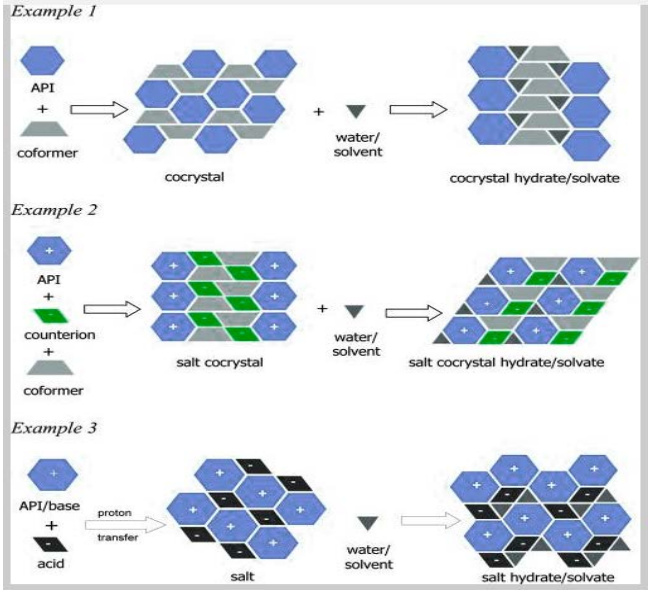

Fig. 2 Common solid state strategies of the active pharmaceuticals (Adopted from Semantic Scholar)

Pharmacokinetic data

Pharmaceutical co-crystals

Pharmaceutical co crystals are unit crystalline elements made up of an API and one or more coformer or other API, at room temperature co crystals are solid. The representation of multicomponent system i.e., co crystals is displayed in the Figure 2 Co crystals are at present the

most dynamically developing group of solid pharmaceutical substances. Pharmacodynamically, co crystal former is a ballast molecule (the same applies to salts), and the GRAS rules apply.

Co-crystals are having more elemental structures whose components interact by weak intermolecular interactions such as hydrogen bonding or other rather than by ion pairing, an important to employ supramolecular synthesis, in particular exploitation of supramolecular heterosynthon is used in designing of co-crystals [3,4]. Supramolecular synthesis is a relatively low-risk strategy, as the approach employs theories of molecular recognition and self-assembly rather than creating covalent bonds. [14]

Advantages:

- Crystalline forms are more stable compared to amorphous form.
- In purification crystallization technique is used.
- Theoretical capability of weakly ionizable/non-ionizable active molecules to form co-crystals [5, 6].

MATERIALS AND METHODS

Materials:

Gabapentin was obtained gift sample from the A-Z Pharmaceuticals at Chennai. Benzoic Acid were purchased from the Sigma-Aldrich chemical Pvt. Ltd, Salicylic were purchased from the Merck specialities Pvt. Ltd and Tartaric Acid were purchased from the Thermo Fisher Scientific India Pvt. Ltd. In current research double distilled water, solvents used for analytical grade

Methods:

Preparation of co-crystal by solvent evaporation:

Gabapentin and co-former were dissolved separately in 5 ml of ethanol with warming and mixed together. Solution was cooled to room temperature and kept for slow evaporation for 6 h. the crystals were isolated by filtration through a membrane (0.45µm) and dried in the air (102) flow process shown in figure 3, 4

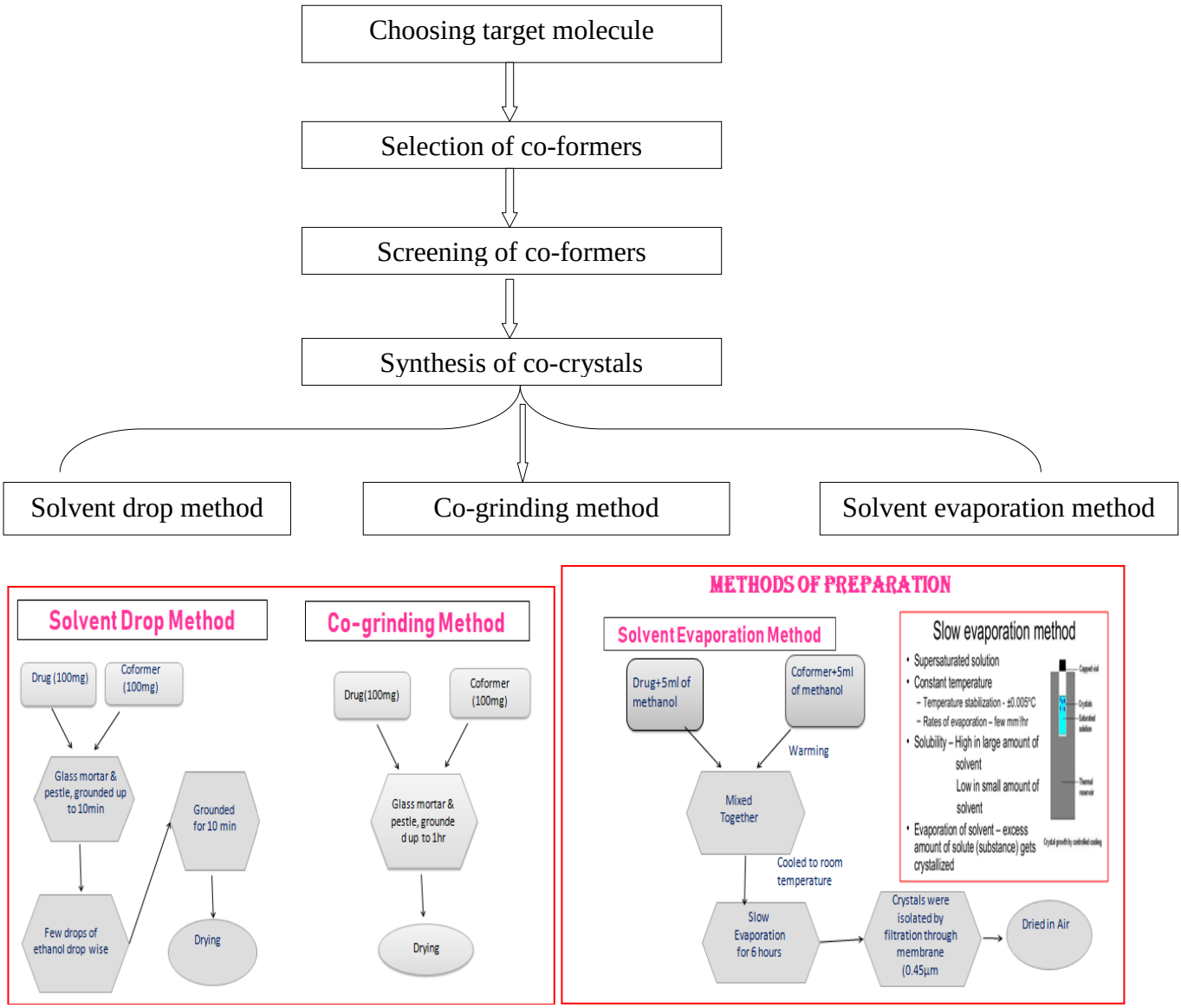

Fig. 3 Flow process of co-crystal synthesis

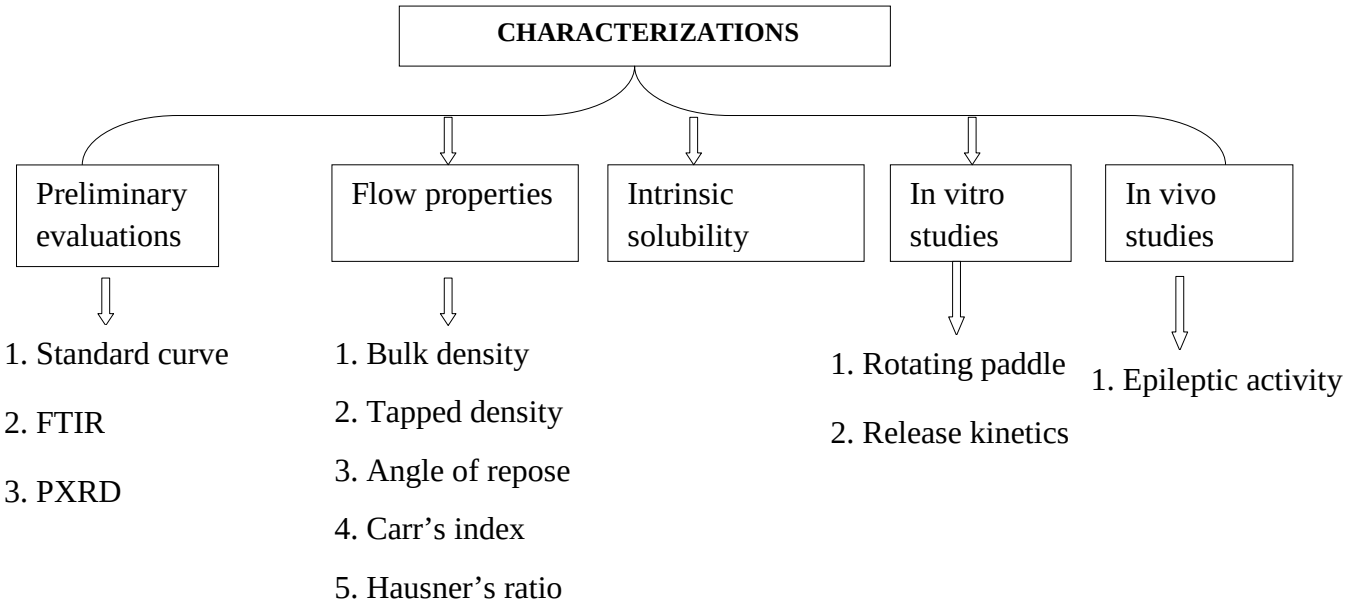

Fig. 4 Flow process of co-crystal Characterizations

Preparation of co-crystal by solvent drop method:
Gabapentin and co-former were taken in glass motor and pestle and grounded up to 10 min. then add solvent (ethanol) few drops in drop wise and again grounded for 10 min. And keep it for drying.

Preparation of co-crystal by co-grinding method:
Gabapentin and co-former were taken in glass motor and pestle and grounded up to 1 hr. and keep it for drying [14].

Standard calibration of drug by UV-Visible spectrophotometer

Calibration Curve of Gabapentin in 0.1N HCL:
Take 5 mg of Gabapentin is dissolved in 100 ml of different medium like 0.1N HCL, distilled water and pH 6.8 phosphate buffer from that 1ml is pipette out and make up to 10 ml, from that 5,10,15,20 and 25 µg/ml solutions prepared and observed at 210nm in case of 0.1N HCL, 315nm in case of distilled water and 270nm in case of pH 6.8 phosphate buffer by using UV-Visible spectrophotometer [7].

Fourier Transform Infrared spectroscopy (FTIR):
FTIR spectra of individual drug, excipients and prepared crystals are recorded by using FTIR spectrophotometer Solvent evaporation, solvent drop and co-grinding methods were employed and the broad spectrum was collected under identical conditions [7].

Powder x ray diffraction (PXRD):
The prepared multicomponent crystal formulations displayed unique crystalline PXRD (Bruker AXSD8 Advance) patterns in comparison to GBP and their respective conformers' like benzoic acid, salicylic acid and tartaric acid indicating the generation of new solid phases [8].

Nuclear Magnetic Resonance Spectroscopy (NMR):
NMR spectroscopy is to observe local magnetic fields around atomic nuclei. It is a vital analysis technique for organic chemists and provides information about the structure of molecule but also determine the content and purity of a sample. [8]

Differential Scanning Calorimetry (DSC):
Pure drug sample and prepared co-crystals are analyzed by NETZSCH DSC 204. The samples (3-5 mg) were placed in sealed non-hermetic aluminum pans and were heated at scanning rate of 10^{o}c min^{-1} over the temperature range of 0- 300^{o}c under dry nitrogen purging (10 ml /min) [9].

Flow properties:

Bulk density:
Bulk density is obtained by adding a known mass of crystals to a graduated cylinder .The bulk density is calculated as mass/volume.

Bulk density
= Weight of crystals/ Bulk volume of crystals (1)

Tapped density:
Tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until the little further volume change is observed. The tapped density is calculated by the final volume of the crystal.

Tapped density
= Weight of crystals/ Tapped volume of crystals (2)

Angle of repose:
The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. Commonly used method is to suspend the granules of the material from a funnel on a flat surface and measure the included angle with the horizontal.

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

Where, h= height of the heap
r = Radius of the heap

Carr's Index (CI):
Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$CI = (T_D-B_D)/ T_D x100$ (4)

Where T_D = Tapped density

B_D = Bulk density

Hausner's Ratio:

It indicates the flow properties of the powder and ratio of tapped density to the bulk density of the powder or granules [10]

Hausner's Ratio

= Tapped density / Bulk density (5)

Intrinsic solubility:

During saturation solubility study, an excess amount of drug and prepared Co-crystals was placed within the vials containing 10 ml of various pH Medias. The vials were agitated in incubator shaker (100 agitations/min) for 4 hours at room temperature. The solution was filtered through a membrane (0.45µm) and the quantity of the drug dissolved was analyzed UV-spectrophotometrically [11]

In vitro dissolution studies

The in vitro dissolution studies were performed in eight-station USP type 2 paddle dissolution equipment (Lab India, Model Disso 2000). Dissolution studies were carried out using 900ml of 0.1 N HCL, at 37± 0.5˚C. 5 ml of sample was withdrawn an appropriate after suitable time interval and replaced when with 5 ml of recent solution. The solutions were instantly filtered and diluted and the concentration of co-crystal were determined spectrophotometrically at respective λ max [11]

Release kinetics

The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to, Zero order, First order, Higuchi matrix and peppas. In this by comparing the r-values obtained, the best-fit model was selected.

Zero Order Kinetics

The zero order rate equation describes the systems where the drug release rate is independent of its concentration. A plot of % cumulative drug release vs. time is linear.

$C = Ko\ t$ **(6)**

Where,

Ko = Zero order release constant.

T = Time

First Order Kinetics

The first order equation describes the system where the drug release rate is dependent of its concentration. A plot of log % drug remaining vs. time is linear.

$Log\ C = log\ Co + Kt /2.303$ **(7)**

Where,

Co = Initial concentration of drug

K = First order rate constant.

Higuchi Model:

Higuchi model was developed on the basis of fick's law and it describes the fraction of drug release from a matrix is proportional to square root of time. A plot of % drug released vs. square root of time is linear. The higuchi equation is

$Q = Kt ½$ **(8)**

Where,

K= Constant ; T= Time

Peppas Release Model:

In this model the drug release rate is fitted to the following equation

$Ft / F\infty = Kp.\ tn$ **(9)**

Where,

$Ft / F\infty$ = Fraction of drug release,

Kp= Release constant,

t = Drug release time and

n = Diffusion release exponent for the drug release that is dependent on the shape of the matrix dosage form [12].

***In vivo* study**

Male mice (25-30 g) were used. Animals were weighed and placed in standard cages with free access to food and tap water. After 7 days of adaptation to laboratory conditions, the animals were randomly assigned to experimental groups each comprising 5 mice. GBP free base and co crystal compounds were prepared as suspensions in 0.5% carboxymethylcellulose in saline and administered via oral gavage. After 30 minutes of the drug dosing, electro convulsions were produced by current (fixed current 50 mA, 0.2 s stimulus duration) delivered to saline-wetted eyes via corneal electrodes from an electroshock apparatus (Techno, India). The criterion for the occurrence of seizure activity was the tonic hind limb extension (HLE i.e., the hind limbs of animals outstretched 180° to the plane of the body axis). The protective activity of GBP free base and its multicomponent forms was determined as the median effective dose (ED5o value in mg/kg) against MES induced seizures. Sufficient animals were tested over a range of drug doses of compound (10, 20, and 30.0 mg/kg of GBP-TA Formulation) to provide data for calculation of ED50 values [13].

RESULTS AND DISCUSSION

Standard Calibration curve of Gabapentin:

In a simple linear regression analysis only a straight line relation between two variables is examined. Calibration curve constructed for concentration range of 5 -25 ug/ml in different medium obeyed Beer Lambert's law. The drug showed linearity in the range of 5 - 25 µg/ml. with a correlation coefficient of 0.998 in 0.1 N HCl. Overall linear regression values are tabulated in Table1 and graph represented in figure 5, 6 and 7.

FTIR:

The FTIR spectrum of pure Gabapentin showed a strong C-H Stretching (Alkane) band around 2918.153 cm^{-1}, H-C=C Stretching 2855.374 cm^{-1}, N-H Bending C-CL bending at 1541.543 cm^{-1}. The FTIR spectrum of prepared crystal formulations recorded using Micro labs Agilent technologies Cary 630 FTIR. In case of GBP-BA CF1 showed a strong H-C=C Stretching at 2846.875 cm^{-1}. In case of GBP-Salicylic acid CF I showed a strong, H-C=C Stretching at 2923.996 cm^{-1},. While in case of GBP-Tartaric acid CF I showed a strong H-C=C Stretching at 2931.893 cm^{-1}. The shifting values are indicating formation of new co-crystal phase, represented in figure 8.

Table No. 1. Linear regression analysis for Gabapentin by UV-visible spectrophotometer:

S. No	Medium	R^2	m	C
1	pH 1.2 (0.1N HCl)	0.998	0.028	0.001
2	pH 6.8 Phosphate Buffer	0.995	0.032	0.009
3	Distilled Water	0.998	0.033	0.001

Table No. 2. Flow properties of pure drug and prepared co-crystal formulations

Formulation code	BD [g/cc]	TD [g/cc]	CI [%]	HR	AR [θ]	Flow properties
GBP pure	0.50 ± 0.045	0.58 ± 0.04	13.56 ± 0.8	1.14 ± 0.09	33.69 ± 0.19	Passable
GBP-BA CF I	0.46 ± 0.035	0.49 ± 0.07	11.00 ± 0.6	1.12 ± 0.04	23.57 ± 0.15	Excellent
GBP-BA CF II	0.47 ± 0.065	0.53 ± 0.08	12.11± 0.7	1.13 ± 0.07	25.52 ± 0.17	Good
GBP-BA CF III	0.43± 0.055	0.54± 0.05	15.98± 0.5	1.19 ± 0.05	31.43 ± 0.19	Passable
GBP-SA CF I	0.45 ± 0.044	0.51 ± 0.09	11.58 ± 0.8	1.12 ± 0.08	22.44 ± 0.11	Excellent
GBP-SA CF II	0.44 ± 0.054	0.52± 0.07	14.68 ± 0.6	1.17 ± 0.06	24.54 ± 0.14	Good
GBP-SA CF III	0.40 ± 0.064	0.51 ± 0.08	15.0 ± 0.7	1.18 ± 0.07	30.85 ± 0.16	Passable
GBP-TA CF I	0.42 ± 0.041	0.50 ± 0.11	14.48 ± 0.54	1.17 ± 0.12	24.52 ± 0.15	Excellent
GBP-TA CF II	0.45 ± 0.061	0.50± 0.14	13.0± 0.58	1.14± 0.14	25.12 ± 0.17	Good
GBP-TA CF III	0.40± 0.051	0.49 ± 0.12	16.64± 0.56	1.20 ± 0.13	30.24 ± 0.19	Passable

(N=3 ± S.D); BD-Bulk density; TD- Tapped density; CI- Carr's index; AR- Angle of repose; CF1- Solvent Drop Method; CF II-Co-Grinding Method; CFIII-Solvent Evaporation

Table No. 3. Dissolution data of pure drug and its co-crystal forms in pH 1.2 (0.1 N HCl)

Time	GBP pure	GBP-BA CF I	GBP-BA CF II	GBP-BA CF III	GBP-SA CF I	GBP-SA CF II	GBP-SA CF III	GBP-TA CF I	GBP-TA CF II	GBP-TA CF III
0	0	0	0	0	0	0	0	0	0	0
30	7.7±0.14	11.3±0.15	10.2±0.14	14.1±0.42	10.8±0.43	9.1±0.16	8±0.12	8.6±	16.9±0.28	13±0.11
60	11.2±0.26	23±1.13	22.5±1.19	25.2±1.19	19.7±0.52	25.2±0.29	12.2±0.18	22.5±	26.6±0.42	24.7±0.43
90	18.3±0.11	31.1±1.15	34.7±1.18	33±1.20	27.5±0.75	29.7±1.13	21.4±0.43	30.2±1.11	29.7±1.09	30.8±1.12
120	28.9±1.19	46.9±0.21	46.1±1.16	45.3±1.28	41.9±1.18	37.8±1.14	26.9±0.55	42.5±1.13	35±1.11	43.3±1.13
150	33.5±2.11	50.3±1.24	57.5±1.15	58.1±1.17	50.6±1.29	43.9±1.16	30.3±1.09	53.3±1.15	46.7±1.13	54.7±1.18
180	40± 2.14	65.9±1.43	68.7±1.14	68.1±1.19	61.4±1.17	55.3±1.18	41.4±1.12	60.9±1.16	52.3±1.15	65.3±1.17
210	49.1±1.54	77.6±1.46	80.4±1.15	74.2±1.12	64.5±1.23	75.3±1.17	58.6±1.14	66.5±1.17	69.2±1.17	74.8±1.16
240	55± 1.53	85.1±1.49	89.3±1.23	87.2±1.14	75.4±1.43	82.6±1.4	73.7±1.18	75.4±0.18	82±1.19	81±1.20
270	70.1±1.25	90.2±1.54	90.4±1.26	88.9±1.15	88.8±1.17	85.3±1.15	79.1±1.17	89.3±1.19	84.8±1.21	87.2±1.23
300	79.3±1.28	91.5±1.34	92.5±1.42	91.7±1.21	89.1±1.21	89.2±1.21	85.5±1.19	90.8±1.22	89.9±1.24	90.6±1.11
330	81.2±1.36	94.7±1.22	94.3±1.13	93.6±1.15	91.4±1.18	91.4±1.13	92±1.0	92.6±1.25	93.2±1.26	92.4±1.13
360	86.3±1.45	97.7±1.23	97.2±1.11	95.5±1.14	95.2±1.16	96.3±1.14	96.5±1.23	94.4±1.29	95. ±1.29	98.3±1.18

(N=3 ± S.D); GBP-Gabapentin; BA-Benzoic Acid; SA- Salicylic Acid; TA- Tartaric Acid; ; CF1- Solvent Drop Method; CF II-Co-Grinding Method; CFIII-Solvent Evaporation

PXRD Analysis:

The powder diffraction spectra of pure GBP shows characteristic peak at 17.412^0 which is 100 % relative intensity which is different from GBP-BA CF III showing characteristic peaks at 7.924^0 while in case of GBP-SA CF III showing characteristic peaks at 6.178^0 and GBP-TA CF III showing characteristic peaks at17.248^0. But GBP-SA CF III showing a less characteristic peaks comparison to other two formulations represented in figure 9

NMR :

The NMR spectrum of prepared crystal formulations by solvent evaporation method.In case of pure GBP showed a strong 2.241 cm^{-1} at Methyl ketone, In case of GBP-Salicylic acid CF III showing a same transfer group 2.399 cm^{-1} at Methyl ketone and. While in case of GBP-Tartaric acid CF III showing a same transfer 2.336 cm^{-1}at Methyl ketone, the shifting values are indicating formation of co-crystal by solvent evaporation method represented in figure 10.

Measurement of flow ability:

The angle of repose of Gabapentin and prepared co-crystals formulations were assessed by fixed funnel method. The solvent drop method crystals (GBP-BA CF I, GBP-SA CF I and GBP-TA CF I) are showing excellent flow properties while compared to co grinding method crystals (GBP-BA CF II, GBP-SA CF II and GBP-TA CF II) and solvent evaporation method crystals (GBP-BA CF III, GBP-SA CF III and GBP-TA CF III) . While in case

of co-grinding method the prepared crystals are showing good flow properties and in case of solvent evaporation method showing passable flow properties represented in Table 2.

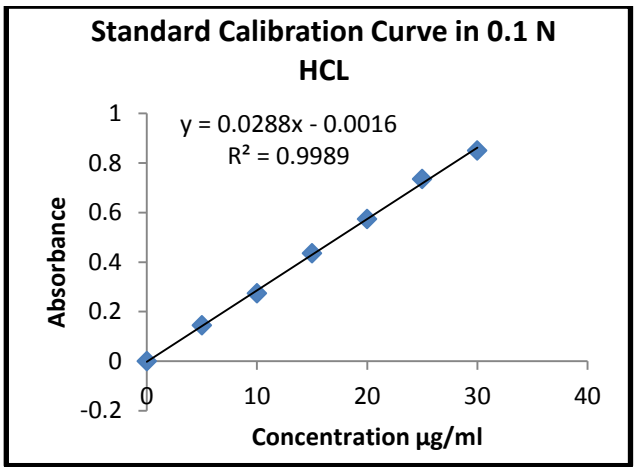

Fig. 5 Standard Calibration curve of Gabapentin in 0.1N HCL

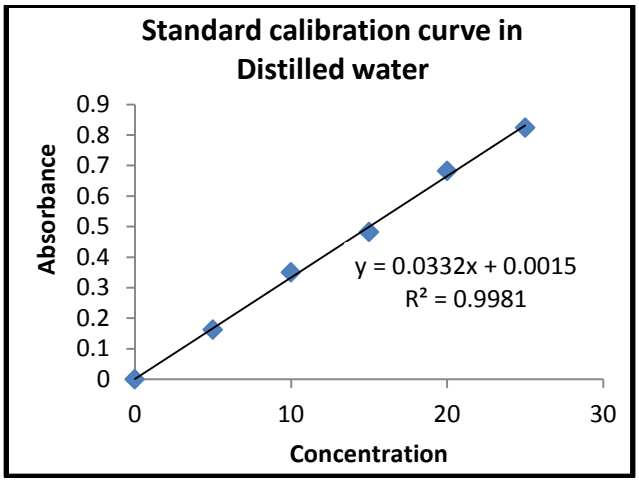

Fig. 6 Calibration curve of Gabapentin in distilled water

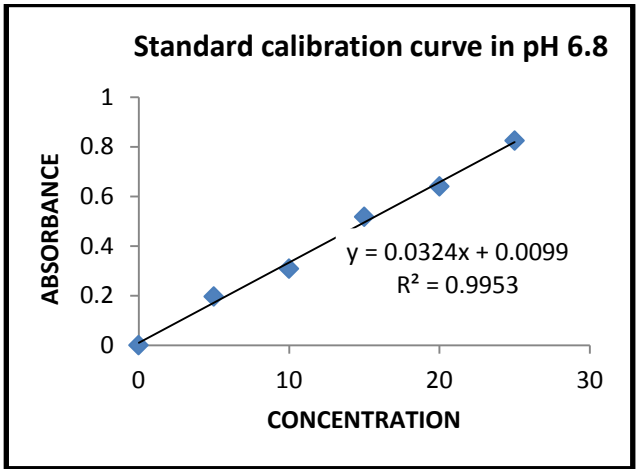

Fig. 7 Calibration curve of Gabapentin in pH 6.8 phosphate buffer

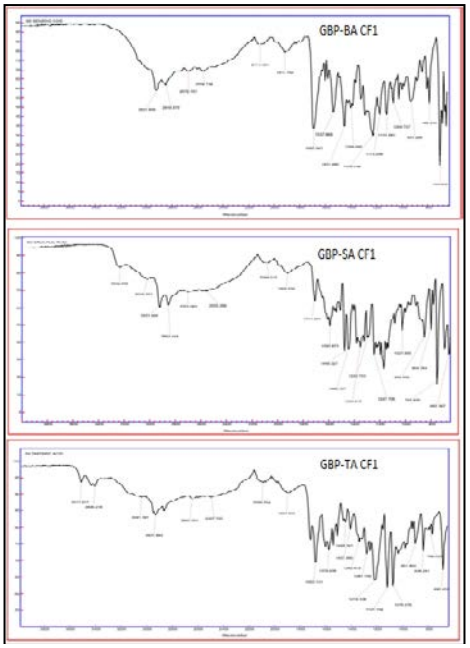

Fig. 8 FTIR of prepared co-crystals A) GAB-BA CF-I; B) GBP-SA CF-I; C) GBP-TA CF-I

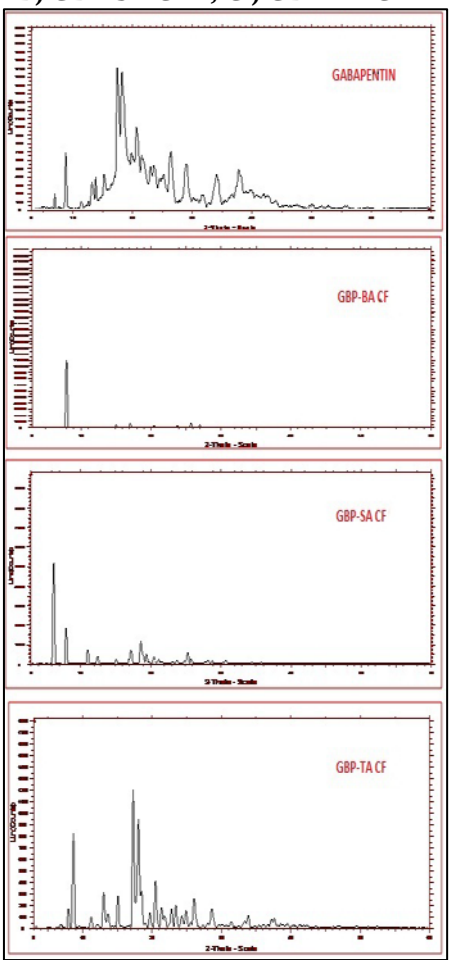

Fig. 9 PXRD analysis of A) GBP-Gabapentin B) GBP-BA CF III- Gabapentin-benzoic acid crystal formulation III C) GBP-SA CF I Gabapentin-Salicylic acid crystal formulation I D) GBP-TA CF III - I Gabapentin-Tartaric acid crystal formulation III

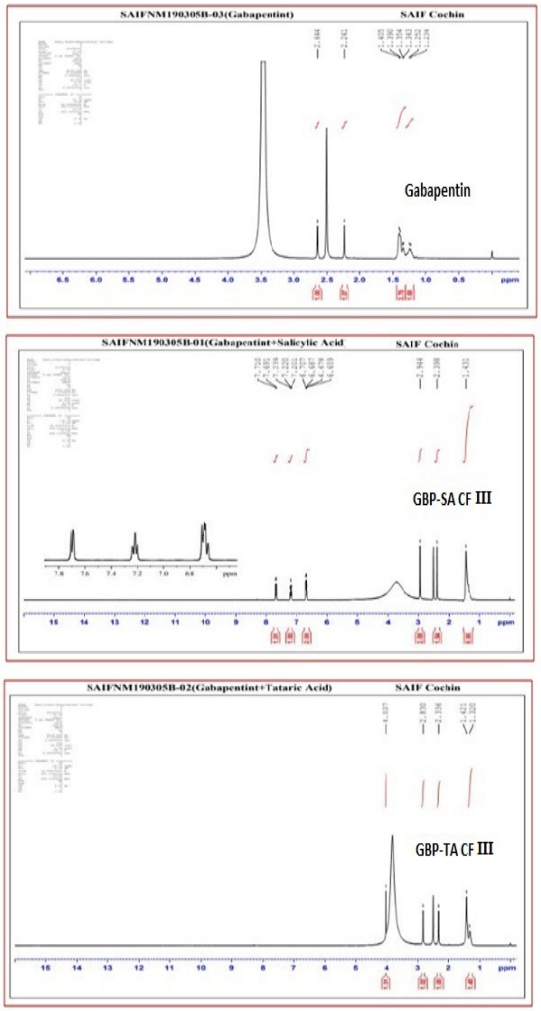

Fig. 10 NMR data of A) Gabapentin , B) Gabapentin-Salicylic acid crystal III and C) Gabapentin- Tartaric acid crystal III by using solvent evaporation method

Saturation solubility:

The prepared multicomponent co-crystal formulations and pure Gabapentin were evaluated for saturation solubility analysis in case of pure Gabapentin showed 5.99 (mg/ml), GBP-TA CF II showed high solubility values 8.10, and 13.52 folds solubility increases compared to pure Gabapentin. By comparing saturation solubility analysis, GBP-TA CF II prepared co-crystals by using the co-grinding method is giving optimum results while compared to other methods like solvent drop method and solvent evaporation method represented in figure 11.

In vitro dissolution Studies

In vitro dissolution studies were carried out in 900 ml of pH 1.2 (0.1 N HCl) at 50 rpm and maintain temperature at 37 ± 0.5˚C dissolution for each formulation are carried out triplicate using eight-station USP type 2 paddle apparatus. GBP pure form releases 86.3% at the end of 360th minute. While in case of prepared co-crystal formulations like GBP-BA CF I, II and III showed drug release at the end of 360th minute are 97.7%, 97.2%and 95.5%In case of GBP-SA CF I, II, and III showed drug release at the end of 360th minute are 95.2%, 96.3% and 96.5%. While in case of GBP-TA CF I, II, III showed drug release at the end of 360th minute are 94.4%. 95.2% and 98.3%. The drug release profile high in GBP-TA CF III (98.3%) at the end of 360th minute represented in figure 12.

The release kinetics were done for prepared co-crystal formulations, in case of zero order the regression value high for GBP-SA CF III (0.984) while in case of GBP-SA CF I showed 0.981. While in case of Peppas release kinetics GBP-TA CF III showed high regression value (0.998) and release exponent showed 0.792 and optimized formulation following non Fickian release mechanism represented in figure 12, 13, 14 and 15. The regression values are high in GBP-TA CF III formulation was selected as optimized used for in vivo study.

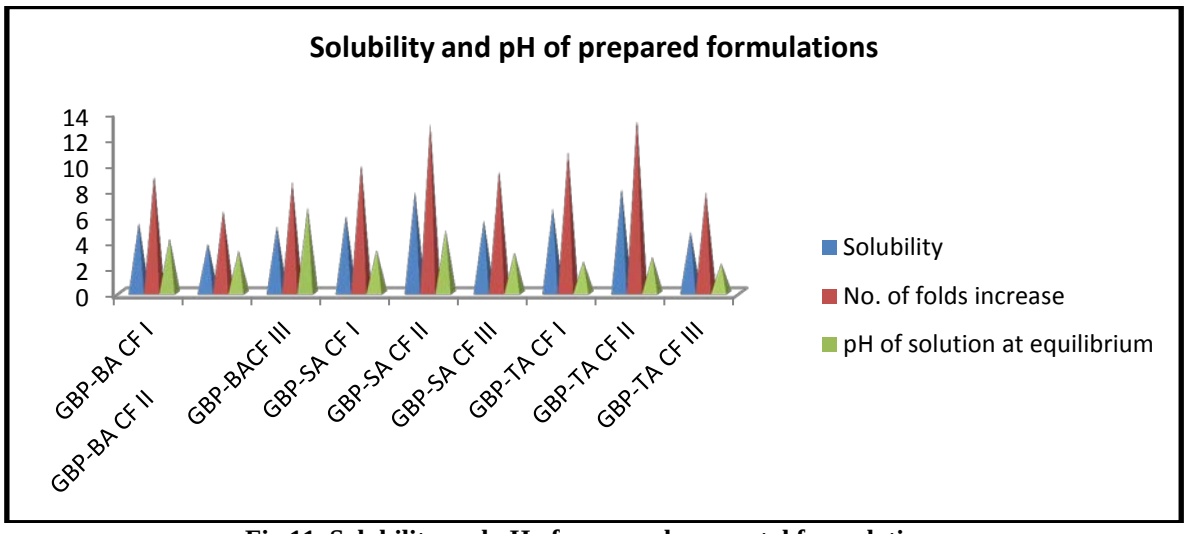

Fig.11. Solubility and pH of prepared co-crystal formulations

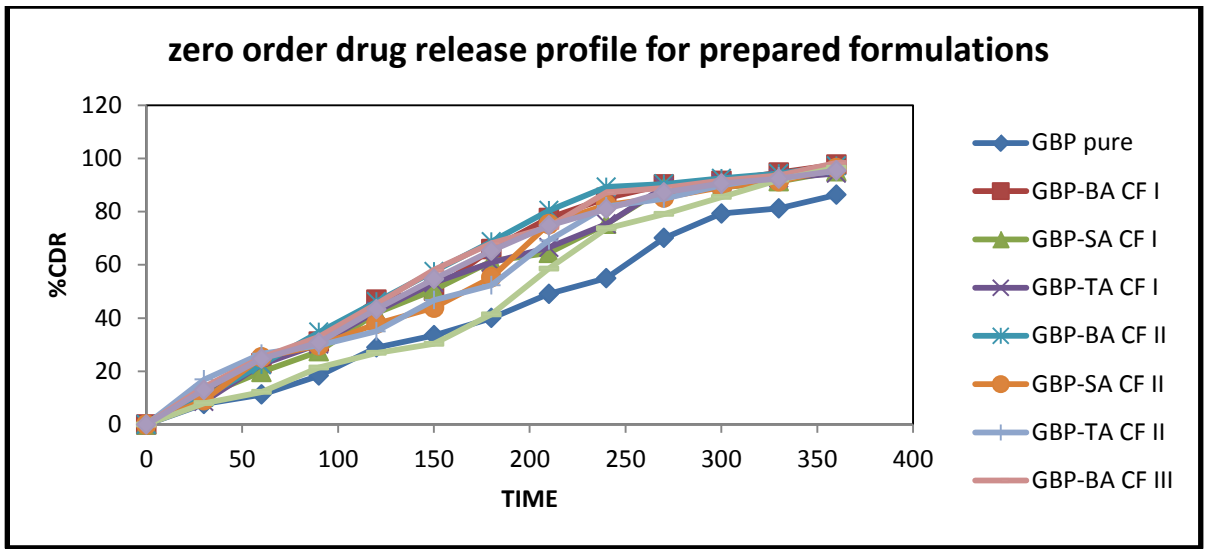

Fig. 12 Zero order release kinetics of GBP and prepared co-crystal formulations

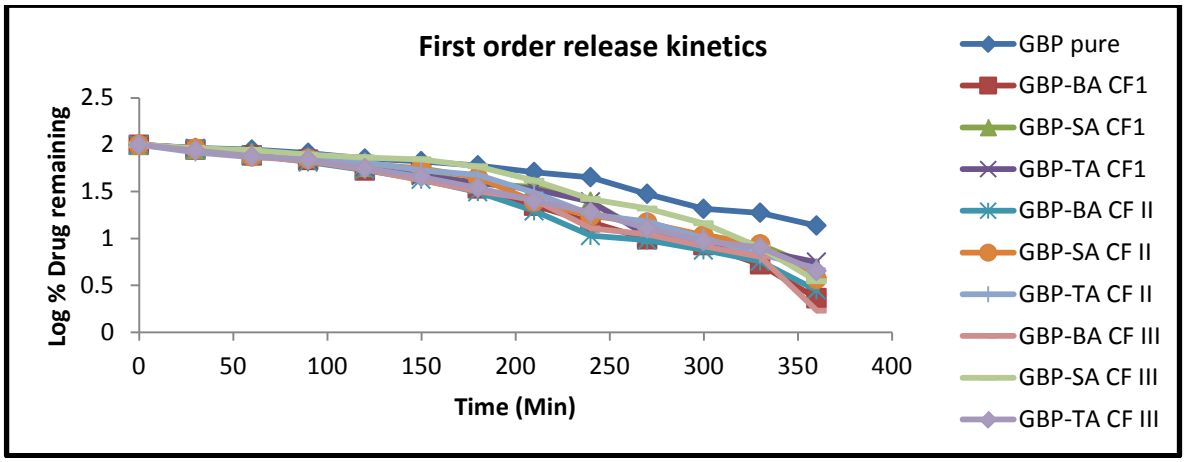

Fig. 13 First order release kinetics of prepared co-crystal formulations

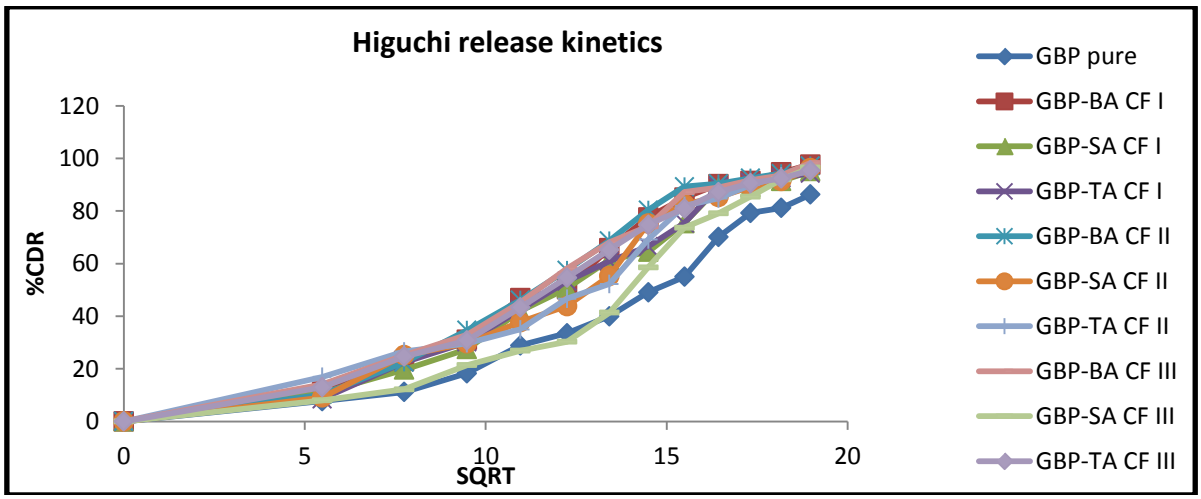

Fig. 14 Higuchi release kinetics of prepared co-crystal formulations

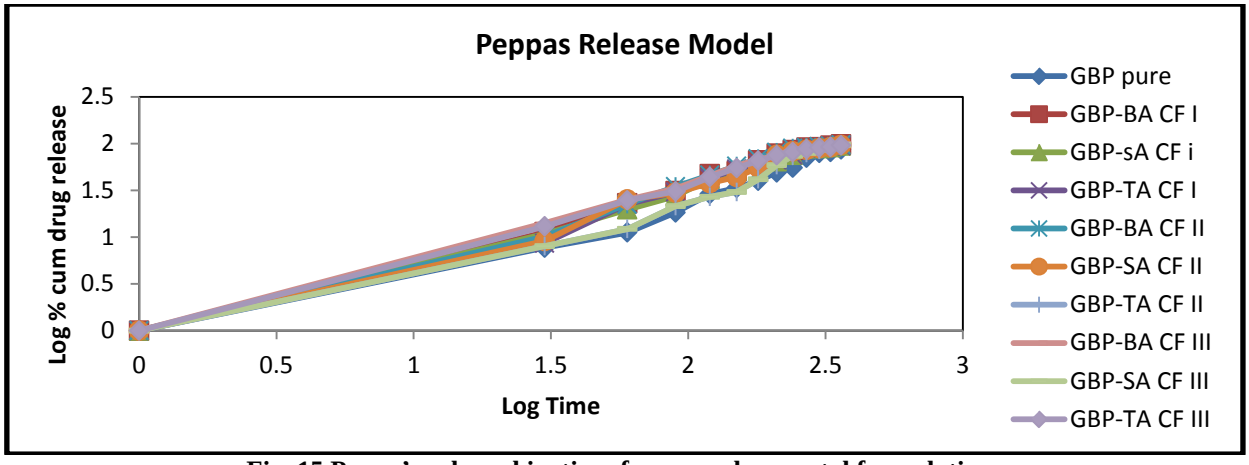

Fig. 15 Peppa's release kinetics of prepared cocrystal formulations

Fig 16 Pictorial representation of *in vivo* study

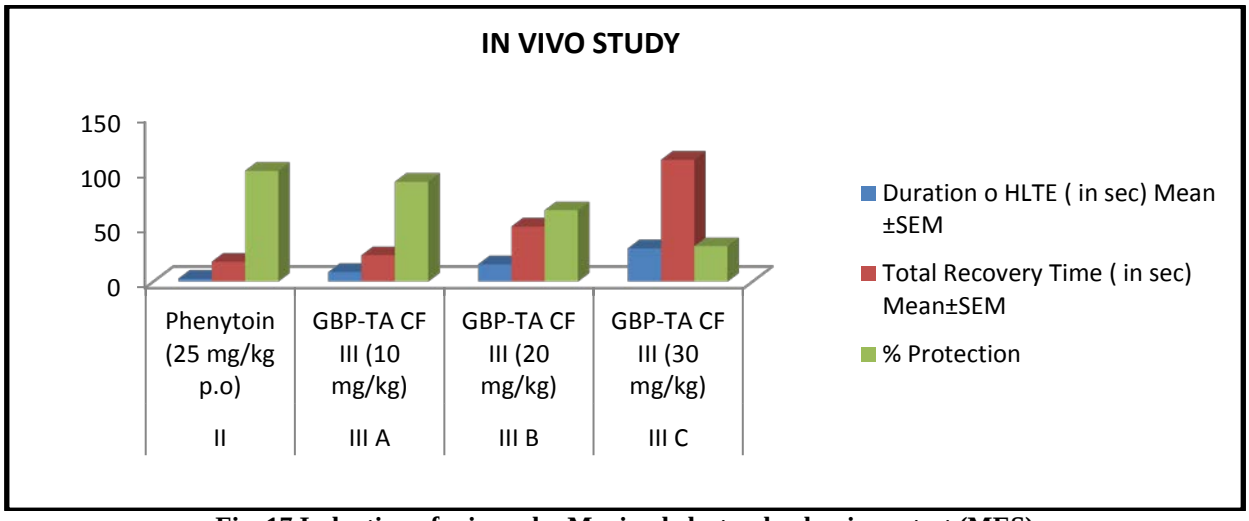

Fig. 17 Induction of seizure by Maximal electroshock seizure test (MES)

In vivo study

The mean duration of total recovery time in the control group (Group I) was 180.33 ± 9.804 seconds. The mean duration of total recovery time was 24, 50 and 110 seconds for groups III A, III B and III C. The percentage protection high in GBP-TA III co crystal formulation dose of 10 mg/kg represented in figure 16, 17.

CONCLUSION

In current research work solvent evaporation is producing best results while compare to other methods. The prepared multicomponent co-crystal formulations and pure Gabapentin were evaluated for saturation solubility analysis in case of pure Gabapentin showed 5.99 (mg/ml), GBP-TA CF II showed high solubility values 8.10, and 13.52 folds solubility increases compared to pure Gabapentin. The solvent drop method crystals are showing excellent flow properties while compared to co grinding method crystals and solvent evaporation method crystals. GBP pure form releases 86.3% at the end of 360^{th} minute while in case of prepared co-crystal formulations. The drug release profile high in GBP-BA CF III (98.3%) at the end of 360^{th} minute. GBP-TA CF III showed high regression value (0.998) and release exponent showed 0.792 and optimized formulation following non Fickian release mechanism. The regression values are high in GBP-TA CF III formulation was selected as optimized and used for in vivo study.

The mean duration of total recovery time was 24, 50 and 110 seconds for 10 mg/kg, 20 mg/kg and 30 mg/kg. The percentage protection high in GBP-TA III co crystal formulation dose of 10 mg/kg compared to other doses. The dose size decreases and percentage protection increasing showing greater control of toxicity.

Acknowledgement

The Authors are thanks full to Vignan's foundation for Science, Technology and Research chairman Dr. Lavu Rathaiah, STIC Cochin, and Sree Vidyanikethan College of Pharmacy management Dr M. Mohanbabu, Principal Dr. Anna Balaji and department of Pharmaceutical Sciences, for providing necessary facilities and infra structure

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