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Modulation of morphology and efficacy of new CB1 receptor antagonist using simple and benign polymeric additives

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The compound **1**, [(1*H*-[1]benzoxepino[5,4-c]pyrazole-3-carboxamide, 8-chloro-1-(2,4-dichlorophenyl)-4,5-dihydro-N-1-piperidinyl], a known CB1 modulator has been synthesized and characterized by IR, NMR and single Crystal X-ray study. The single crystal study of **1** displays a number of halogen bonds leading to 1-D network along with other weak non-covalent interactions. The CB1 modulator **1** inherently possesses extremely low solubility in water, which makes its application as drug difficult, and this may be attributed to multiple halogen bonds present in the crystal structure. A series of polymer additives, which are Generally Regarded As Safe (GRAS), have been explored to investigate whether they can modulate the halogen bond present in **1** through formation of various non-bonded interactions. Surprisingly, these polymers are found to change crystal morphology, crystal packing while retaining efficacy and bioavailability. The polymer molecular weight is found to play a significant role in crystal morphology modification especially in case of polyethylene glycol (PEG). The formation of new polymorphic forms of **1** and modification of halogen bond has been established using powder X-ray diffraction and IR study, respectively, in case of PEG 4000, PVPK-30, PVA polymers and compound **1** adducts.

Keywords: Obesity, CB1 antagonist, crystallography, morphology, *in vivo* efficacy

Obesity, a lifestyle disease, is one of the largest and fastest growing public health problems in the developed and developing world[1]. Obesity is associated with substantial increases in morbidity, premature mortality, impaired quality of life and large healthcare costs[2,3]. Despite continuous effort and research, obesity pharmacotherapy has yielded very little success. Another approach to treat obesity is to regulate the appetite and food intake in animals and humans. A class of compounds, which have been evaluated for the regulation of appetite and food intake in animals and humans, are the cannabinoid receptor modulators (CB1 receptor modulators). Numerous drugs such as Rimonabant hydrochloride, Taranabant, Otenabant, Surinabant and Ibipinabant were developed as potential drugs targeting the cannabinoid receptor type 1 (CB1)[4]. Of these, Rimonabant was approved by the European Medicines Authority (EMA). However reports of serious psychiatric problems (such as anxiety, depression and suicide) led to its withdrawal from the market[5-7]. Despite the withdrawal of several CB1-receptor-antagonist drugs from the market, many researchers believe that neutral antagonists might retain the weight loss advantages, but will be devoid of reported adverse effects[8]. Understandably, the promising approach is to develop agents, preferable without charge, to prevent it to cross the blood-brain barrier[9]. It is postulated that the excessive presence of such drug in brain may leads to many serious psychiatric problems. One such promising CB1 modulator is compound (**1**) [(1*H*-[1]benzoxepino[5,4-c] pyrazole-3-carboxamide, 8-chloro-1-(2,4-dichloro-phenyl)-4,5-dihydro-N-1-piperidinyl, with an EC_{50} 14.5 μM in human CB1 receptor forskolin-induced cAMP assay[10].The compound **1** was expected to be a neutral antagonist since it did not change the forskolin-stimulated cAMP accumulation in CB1-transfected HEK cells up to 10 μM concentration. Therefore, the compound **1** has a great potential for

the treatment of obesity. Unfortunately, the crystalline form of the molecule suffers from poor oral bioavailability and pharmacokinetic profile[11]. The authors have earlier reported a process for the preparation of compound **1** in amorphous form[11]. A well-established approach to change the bioavailability and efficacy of a drug is the formation of salts/co-crystals, which is not suitable for the present study as formation of charged species should be avoided to deter the transportation of drug through blood-brain barrier. Therefore, a different approach is required to improve the physico-chemical properties of compound **1** without bringing any significant change to either its bio-availability or efficacy (Figure 1).

For years, controlling the physical properties of solid APIs through modification of the solid phase without changing the molecular structure of the API itself has remained a prime research interest of academic and industrial research groups[12,13]. One of the most important and most used methods of non-covalent modification of APIs is salt formation, in which the API is neutralized by an acid or a base to make a salt[14]. More recently, co-crystallization (broadly defined as the crystallization of two non-covalently interacting neutral compounds in the same crystal lattice) has also been used for this purpose[15,16]. Co-crystallization has even more scope than salt formation because there appears to be no theoretical limit on the types of APIs that can be incorporated into co-crystals. Researchers have been able to make new co-crystals year after year[17]by combining design strategies such as the concepts of supramolecular synthons with high throughput screening methods such as solvent-assisted grinding.

The synthesis of inorganic and organic materials with a specific size and morphology has recently

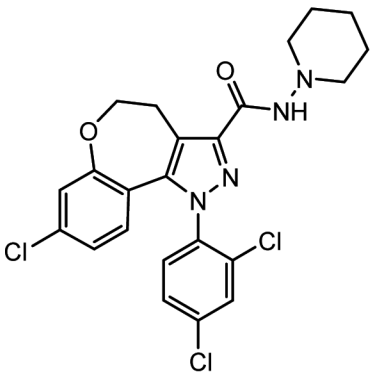

Figure 1 — CB1 inhibitor used for the present study

received much attention in the material science research area. Many routes have been reported to control the crystal growth and eventually modify the morphology of the crystals. For crystal-habit modification, crystals are grown in the presence of naturally occurring soluble additives, which usually adsorb or bind to the crystal faces and influence the crystal growth or morphology[18].

Crystal growth modifiers can be used to achieve a range of outcomes. They can dramatically affect particle shape and size and therefore can be used in a particle engineering sense, i.e. to obtain the desired physical properties of the particles in question. Additives can also inhibit nucleation and growth which has applications such as scale inhibition. They may even increase the rate of crystallization and be used as promoters[19].

The crystal-habit modifiers may be of a very diverse nature, such as multivalent cations, complexes, surface active agents, soluble polymers, biologically active macromolecules, fine particles of sparingly soluble salts, and so on. These crystal modifiers often adsorb selectively on to different crystal faces and retard their growth rates, thereby influencing the final morphology of the crystals. The strategy uses organic additives and/or templates with complex functionalization patterns to control the nucleation, growth, and alignment of inorganic and organic crystals[20].

In the present study, we decided to address few questions related with compound **1** such as why compound **1** has very low bioavailability and what are the factors which influence the overall packing of **1** leading to its inflexible behavior to form different crystalline forms. Efforts were also directed to understand the packing of compound **1** with respect to its various non-covalent interactions present in crystalline state, namely, halogen bond and amide…amide linkage and look for the methods to influence it. In this regards, we decided to study the effect of hydrophilic polymers as additive to compound **1**, which can influence the amide…amide non-covalent interaction and Cl….Cl (halogen bond) by giving additional possibilities of weak non-covalent interactions such as Cl…O, O-H…O, etc. These polymers belong to the GRAS class of polymers and are used extensively in formulation studies.

However, to the best of our knowledge such polymer additives have not been used to bring a

change to crystalline packing and crystal habit modification, simultaneously. In the present work, various GRAS polymer additives such as PVA, PEG and PVP K30, having different molecular weights were used for attempting to change the crystal packing, morphology and maintain the efficacy of compound **1** (Figure 2).

Experimental Section

Synthesis

The compound **1** was prepared as per process described earlier[11]. The polymers used in the present studies were purchased from Sigma-Aldrich, India. Analytical grade solvents were purchased from local suppliers and used without further purification.

Characterization

Thermal Analysis

Thermal analyses of all the compounds were carried out to understand the phase transition and stability of compound **1** with or without polymeric additives. The DSC (Differential Scanning Calorimeter) (Perkin Elmer Model Pyris 1) was used for all the thermal analysis. In a typical analysis, 2 mg to 3 mg of sample was taken in a clean aluminium pan and sealed under inert environment. The heating was done from an initial temperature of 50 °C and the temperature was gradually raised at a heating rate of 10°C /min till 300 °C. Nitrogen gas was used at a flow rate of 20 ml/min.

Powder X-ray Diffraction measurement (PXRD) Method

Powder diffractionmeasurement was carried out on X-ray diffractometer (Rigaku make MF2100) using copper source at 40KV and 30 mA having Ni K_β filter. The 2θ scan of each sample was carried out between 2-40° at scan speed of 4.0° per minute.

Single crystal X-ray studies

Crystal suitable for Single crystal X-ray study of compound 1 was obtained from acetone by slow evaporation method at room temperature. Diffraction data for **1** was collected using MoKα (λ = 0.71073 Å) radiation on Xcalibur, Eos, Gemini diffractometer. Structure of **1** was solved and refined using the Olex 2 software[21,22] and ShelXL[23] refinement package. Graphics were generated using MERCURY 3.9. The structure was solved by direct methods and refined in a routine manner. In all cases, non-hydrogen atoms were treated anisotropically. Whenever possible, the hydrogen atoms were located on a difference Fourier map and refined in routine manner. In other cases, the hydrogen atoms were geometrically fixed.

Scanning electron microscopy (SEM)

The surface morphology of the respective samples was examined under ZEISS, EVO 18, scanning electron microscopy (SEM). Solid samples were evenly dispersed on small segment of microscopic glass slide. Then, they were kept in vacuum desiccators for ~1.5 h and the samples were attached to aluminum sample stubs using double-sided carbon tape and were coated with gold in a sputter coater and observed under SEM at an accelerating voltage of 15 kV. Average diameters were measured on at least 25 randomly chosen crystals at several regions of the samples.

Preparation of crystals of compound 1 with PEG-200 (1A)

Placed 0.500 g (1.017 mmol) of compound **1** in a round bottomed flask, to it was added 5 ml acetone. The suspension was warmed upto 45-50°C in a water bath to get clear solution. To it was added a solution of 20% PEG 200 in acetone (5 ml). The mixture was cooled and left to ambient conditions. Crystals were obtained as colourless blocks after two days, which were separated by filtration.

Preparation of crystals of compound 1 with PEG-300 (1B)

Placed 0.500 g (1.017 mmol) of compound **1** in a round bottomed flask, to it was added 5 ml acetone. The suspension was warmed upto 45-50°C in a water

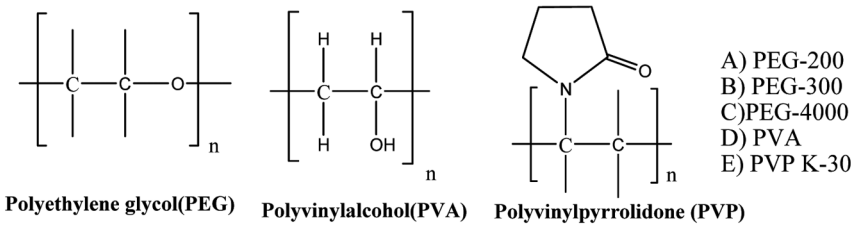

Figure 2 — List of polymers used as crystal habit modifier in the present study

bath to get clear solution. To it was added a solution of 20% PEG 300 in acetone (10 ml). The mixture was cooled and left to ambient conditions. Crystals were obtained as colourless blocks after four days, which were separated by filtration.

Preparation of crystals of compound 1 with PEG-4000 (1C)

A 1:1 mixture (weight by weight, w/w) of compound **1** and PEG 4000 were ground manually in an agate mortar at room temperature for 5 min together with the addition of a few drops of acetone. However, upon removal of the solvent, the components remained as mixtures. Subsequently, a 1:1 mixture (w/w) of compound 1 and PEG 4000 were taken in a round bottomed flask and dissolved in 30 mL of acetone under constant stirring at 50 °C. The solution was filtered and cooled to room temperature. Crystals were obtained after two days which were filtered and dried in a desiccator over silica gel at room temperature.

Similar method was followed for preparation of crystals of compounds **1** with PVA and PVP K-30 polymeric additives.

Biological studies

In vivo efficacy studies of compound (1) and its modified crystals based on their effect on inhibition of fasting induced food intake in C57 mice The animals (C57 mice) were trained for fasting induced food intake. In this procedure, they were allowed access to chow diet from 11 a.m. to 3 p.m. every day, and fasted for rest 20 hours of the day. They were randomized based on their intake, when their daily four hour intake was consistent for two consecutive days. On the day of experiment, the mice were administered the test compounds formulated in saline by intraperitoneal route. The food intake was measured for next four hours, and for subsequent 20 hours. The percent inhibition in the food intake was calculated based on the vehicle control group.

Results and Discussion

The compound **1** was synthesized by the reported procedure and characterized[11]. The polymer and compound **1** adducts were synthesized and subjected to various characterization and analysis such as crystallinity, differences in their melting points with respect to pure compound, changes in their crystal morphology using polarizing microscope and SEM of the modified crystals were compared with the parent compound **1** and efficacies of the modified crystals were compared with pure compound. Effort were also directed to understand the role of polymeric additives on crystal morphology and packing of the compound **1**.

Single crystal X-ray study of 1

The compound **1** was crystallized out from acetone under slow solvent evaporation method at room temperature and it crystallized in triclinic crystal system with space group P-1. The asymmetric unit contains one molecule of compound **1**, which displayed multiple non-covalent interactions, such as Cl….Cl, C-H…O, etc., leading to three dimensional network. One of the prominent halogen….halogen interactions in compound **1** formed 0-D network (zero-dimensional) (Figure 3A) and the another Cl…Cl interaction extended the overall packing of 1 to 1D (one-dimensional) (Figure 3B). The number of secondary interactions such as C-H…O, van der Waals forces, extended the packing of 1 to 3-D(three dimensional). (See supporting information for detailed crystallographic data Table S1).

IR study

IR studies were carried out to establish the nature of weak interactions (hydrogen bonding or halogen bonding) between compound **1** and polymer adducts (**1C**-**1E**). IR frequency of aromatic C-Cl bond (strong peak at 819 cm^{-1}) of **1** changed to bifurcated peak, i.e. 817 and 812 cm^{-1} in certain polymer adducts namely

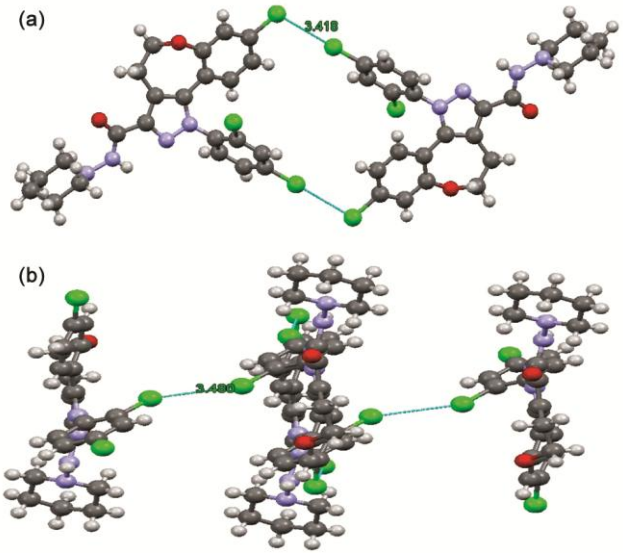

Figure 3 — (A) Intermolecular halogen bonding leading to zero-dimensional network of 1 (B) One dimensional halogen bonded network of 1

(**1C**, **1D** and **1E**). The slight change in position and nature of IR frequency is interpreted as the formation of hydrogen/halogen bonded network.[24] However, no significant change in C=O frequency of amide functional group in 1 and **1A-1E** polymer adducts were noticed. The formation of weak non-covalent bonds between the chlorine atoms of compounds **1** with the polymers, leading to change in crystalline packing as well as morphological change especially in polymer adducts **1C**, **1D** and **1E** [see supporting information, Figure S1] is being proposed, based on the following observations.

Morphology

The crystals of **1** appeared to be well defined rectangular in shape with smooth surface under microscope [See supporting information Figure S2(A)]. Surprisingly, no well-defined crystalline substance was obtained using PEG 200 as additive (**1A**). When compound 1 was crystallized with PEG 300 (**1B**), no significant change in morphology was observed under polarizing microscope [See supporting information Figure S2(B)]. Surprisingly, crystallization of **1** with each of PEG 4000 (1C), PVA (1D) and PVP K-30 (1E), changed the crystal morphologies significantly i.e. from smooth tubular architecture to rough irregular shaped crystals [See supporting information Figures S2(C) to S2(E)]. To visualize the morphologies of the crystals formed in the presence of various polymeric additives thoroughly, SEM analysis was carried out. SEM images of **1** and **1B-1E** corroborates well with the polarizing microscope studies. Crystals of **1** obtained in the presence of PEG 300 polymer additive [Figure 4(B)] exhibited similar morphology as pure form of compound **1** in SEM analysis [Figure 4(A)], while, use of PEG 4000, PVA and PVP K-30, significantly changed the morphology of the crystals [Figure 4C–E]. These studies suggest that the molecular weight of polymer (PEG polymeric additives) as well as the functional groups in the polymer additive (PVA and PVP K30) may play a role in modifying the crystal morphology of **1**.

Powder X-ray diffraction study

In order to understand whether there is any change in crystalline packing of compound **1** in presence and absence of polymeric additives powder x- ray diffractogram (PXRD) of **1** and the polymeric adducts (**1C-1E**) were recorded. The XRD pattern of crystalline **1** is provided in Figure 5A. There was no change in the XRD pattern when PEG 300 was used. This further confirms that PEG 300 did not change the morphology or the crystalline structure of compound **1**.

However, with each of PEG-4000, PVA and PVPK-30, the XRD pattern changed substantially from the PXRD pattern of **1** [Figure 5(C) to Figure 5(E)] (see supporting information Table S2 for a comparison of the peaks with highest intensities for compounds **1** and the polymer adducts **1C-1E**]. This clearly indicates that these polymers were able to modify both the morphologies as well as the crystalline packing of compound **1**.

Thermal Analysis

The DSC thermogram of compound **1** displayed a sharp peak at 199.93 °C, with an onset temperature of 198 °C [See supporting information figure S3(A)] . The DSC thermogram using PEG-300 did not show any difference from that of **1**. The DSC thermogram of the crystal obtained with PEG-4000 showed one sharp endotherm at 61.81 °C and a second small peak at 197.6 °C [See supporting information figure S3(B)]. The former peak clearly indicates that the PEG-4000 was loosely bound to the compound **1**, thereby providing the endothermic peak close to its melting point (54-58 °C). Coupled with the fact that

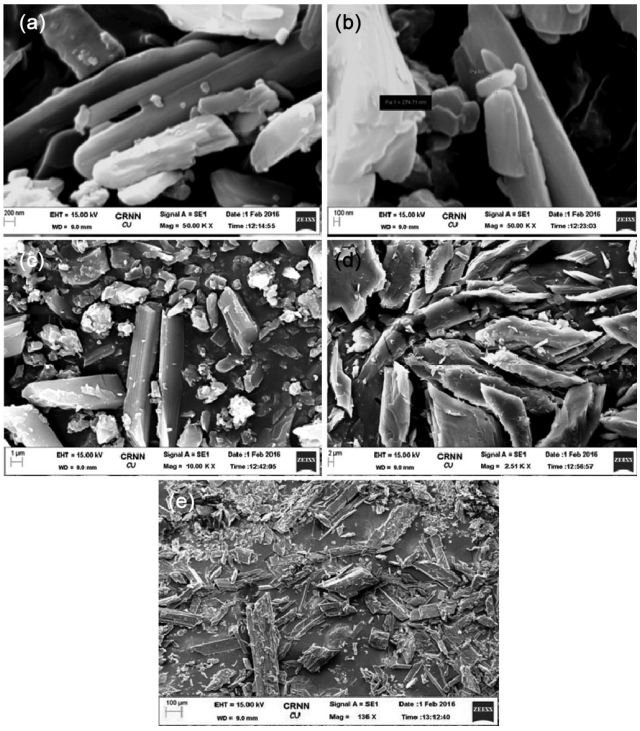

Figure 4 — SEM images of crystal morphology of (A) 1, (B) 1B (PEG-300), (C) 1C (PEG 4000), (D) 1D (PVA) and (E) 1E (PVP K-30)

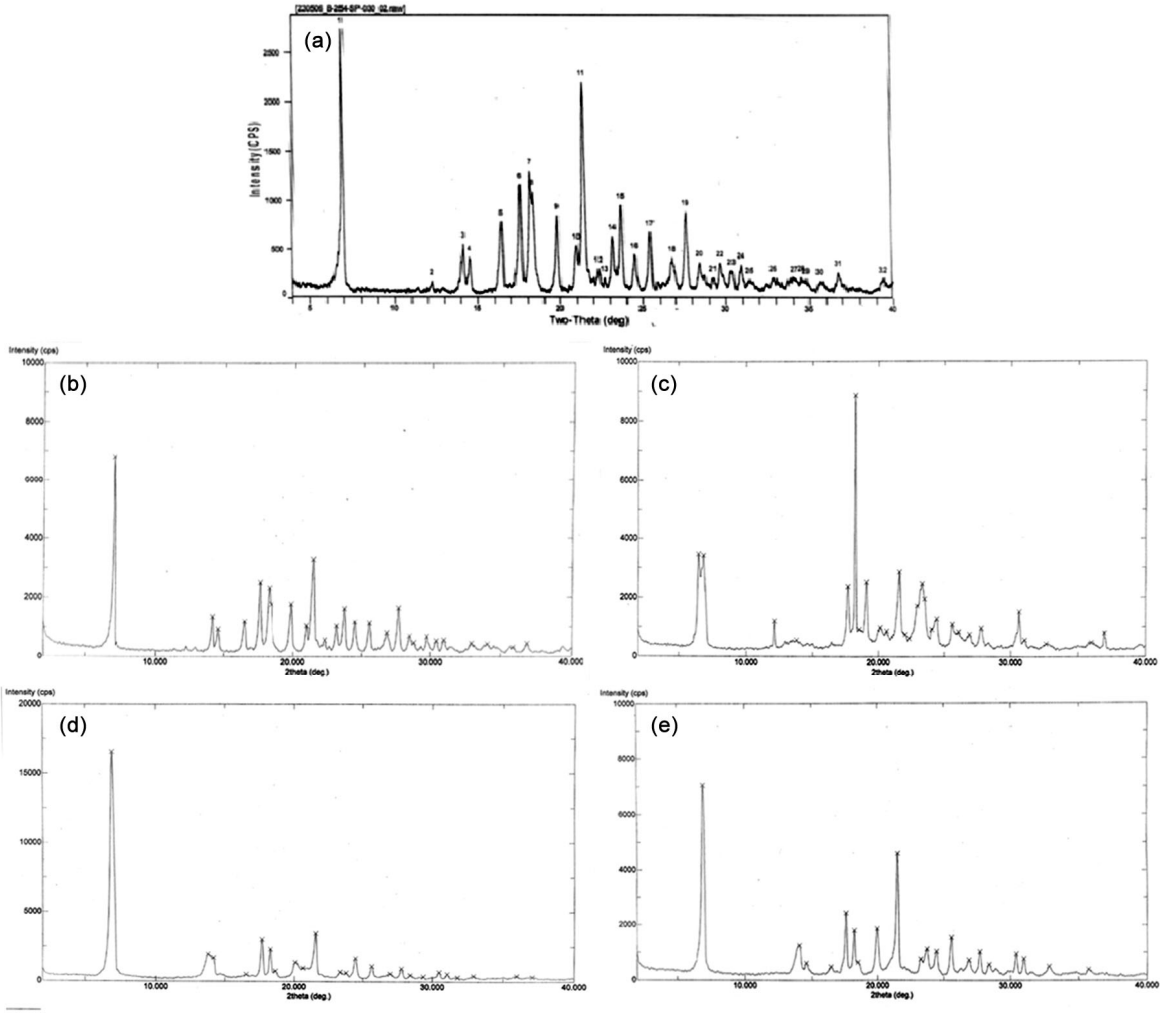

Figure 5 — Powder X-ray diffractogram of (a) 1 , (b) 1B (PEG-300) , (c) 1C (PEG-4000), (d) 1D (PVA), (e) 1E (PVP K-30)

the XRD pattern has changed, one can conclude that the PEG-4000 may have formed a co-crystal with the compound **1**. The second endotherm at 197.6 °C also supports the formation of a co-crystal.

Interestingly, the DSC thermogram of the crystals obtained using PVA and PVPK-30, showed a single endotherm peak at 199.32 and 199.19 °C respectively [See supporting information figureS2]. This clearly rules out the formation of any co-crystal. The formation of alternate polymorphic forms is established based on the PXRD pattern of **1D** and **1E**.

Solubility studies

Saturated solubility studies of the samples were performed in water at room temperature for 24 hours. The solubility of compound **1** in water did not change when crystallized from different organic polymers. Therefore, for the compound **1**, making of the amorphous form is the only way to improve its solubility in water. Interestingly, polymers were able to solubilize the compound **1**. These polymers being of the GRAS family, such solutions can be used for conducting *in vivo* studies and crystal adducts so obtained could be used for further development studies.

***In vivo* efficacy study**

The effect of the modified compounds of (**1**) was studied on inhibition of fasting induced food intake in C57 mice after single intraperitoneal dose at 30mg/kg. The results are provided in Table I.

The observed results (mean ± SD, n=5) indicate that there is reduction in the fasting induced food intake after the test compound administration. The reduction was prominent for the first four hours.

Table I — Effect of compound **1** and its various polymeric adducts on food intake of C57 mice

S. No.	Treatment 30 mg/Kg	Food intake (g) 4 h						Food intake (g) 20 h					
		Feed Consumption in 4 h (g)			% change in feed consumption Versus control			Feed consumption In 20 h (g)			% change in feed consumption versus control		
1	Vehicle Control (IP)	4.5	±	1.4				8.6	±	1.4			
2	Compound 1	3.4	±	0.2	-24.4	±	7.74	7.5	±	0.5	-12.8	±	2.25
3	1B (1+ PEG-300)	3.3	±	0.8	-26.7	±	10.5	8.0	±	0.8	-6.98	±	1.33
4	1C (1+ PEG-4000)	3.3	±	0.8	-26.7	±	10.5	7.5	±	0.5	-12.8	±	2.25
5	1D (1+ PVA)	3.2	±	0.4	-28.9	±	9.7	7.9	±	0.4	-8.14	±	1.39
6	1E (1 + PVP K30)	3.3	±	0.4	-26.7	±	8.9	7.9	±	0.7	-8.14	±	1.50

However, there was no significant difference amongst the different treatment groups.

Conclusions

Crystal structure of **1** showed presence of halogen bonds leading to 1D network and understandably, the halogen bonds will play prominent role in the physico-chemical properties of **1**. GRAS polymeric additives, such as PEG, PVA, PVP K30, with functional groups capable of forming weak non-covalent interactions with **1** were selected and successfully used to carry out morphological and polymorphic changes to **1**. The molecular weight of the polymer, in case of the PEG class of polymers, was found to be playing a role in changing the morphology and crystalline packing of **1.** Thus,PEG-200 and PEG 300 were found to be less effective as compared with PEG-4000. Understandably, the high molecular weight polymers can adsorb better and cover a large surface area of the compound **1** to bring a significant morphological change. Polymeric crystal habit modifiers, especially PEG-4000, PVA and PVP K30, were also capable of forming new polymeric forms of **1**. Surprisingly, such change in crystal forms of **1** did not have any effect on either the solubility or the *in vivo* efficacy of the modified compounds. Such polymers may therefore be used to change the crystalline forms of the compounds without affecting the biological properties of the compound. IR spectra of compound **1** in presence and absence of polymeric additives displayed changes in C-Cl stretching frequency from strong peak (pure form) to bifurcated peaks (polymeric additives, **1C**-**1E**) establishing the change in halogen bonding pattern. The formation of new polymorphic form of **1** in presence of polymeric additives was further established with the help of PXRD and DSC analysis. The present study opens a window of opportunity to tune the morphology, crystal packing without effecting the efficacy of an API using GRAS polymeric additives.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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