Cyclodextrin Ternary Inclusion Complexation: A Strategy to Improve Solubility of Poorly Soluble Drugs

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ABSTRACT

Cyclodextrins (CDs) consist of D- glucopyranoside units that are linked together by glycosidic bonds to form cyclic oligosaccharides. They are mainly employed to ameliorate the physicochemical properties and biological properties of poorly aqueous soluble drugs by the formation of inclusion complexes between the CD and drug. Inclusion complex formation requires the host molecules to fit completely or partially within the CD cavity. The uncomplicated settlement of guest molecules within the CD cavity, therapeutic dose, toxicity and stoichiometry all change according to the physicochemical properties of the guest and host molecules. However, dosage formed volume depends on the amount of CD required. So high amount of CD used leads to high dosage formed volume. Thus, it is necessary to improve the solubilization efficiency in order to use lesser amounts of CD. This could be reached by adding small amounts of water-soluble substances such as polymers, organic acids, amino acids, co-solvents, etc. to the inclusion complex. This review mainly focused on the aspects related to the formation of drugs and CDs' inclusion complex by using different types of water-soluble substances to optimize the amount of CD used in the complexation in order to improve drug solubility, and decrease the bulk of dosage form.

Key Words: Cyclodextrins, Ternary Complex, Auxiliary Substances, Solubility, Complexation.

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INTRODUCTION

Drug dependence and tolerance is becoming an enormous mental health problem and physical effects worldwide and significantly affect the society [1]. And among many factors, aqueous solubility is of essential importance in the production of a sufficiently safe and effective drug delivery system, because formulation, absorption and the clinical response of a drug are all dependent on drug solubility. Many drugs have low water solubility due to the increasing use of lipophilic molecules in the treatment which also tends to increase more. However, many drugs have low water solubility due to the increasing use of lipophilic molecules in treatment which also tends to increase more [2]. Thus, among many different techniques to improve water solubility, the formation of inclusion complex with cyclodextrins (CDs) can be used. Cyclodextrins (CDs) consist of D- glucopyranoside units that are linked together by glycosidic bonds to form cyclic oligosaccharides. The most noticeable property of CDs is their ability to adjust to the physicochemical characteristics of drug molecules after being accommodated within their internal cavity to form what known as inclusion complexes [3].

After the formation of inclusion complexes, formulation can be obtained with faster dissolution rate, and shorter drug release time, and also more efficient absorption, which are the typical characteristics of inclusion complex. This can be translated to improved oral bioavailability and increasing biological activity, which will lead to the reduction of drug dosage [4]. However, because guest molecules need to fit completely or partially within the CD internal cavity, the use of CDs is limited in some

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cases. The easy accommodation of guest molecules within the CDs' internal cavity, therapeutic dose, toxicity of CDs, and stoichiometry all change according to the physicochemical properties of the guest and host molecules [5].

A very critical stage in the applicability of the formulation of CD inclusion complex is the increase in the formulation volume. When the molecular weights of the drug are 200-400 g/mol and the CD is 1200-1500 g/mol, it can be considered that 1 g of solid complex reflects 100-250 mg of the drug. So, the applicability of CDs with oral solid dosage forms is limited to drug doses less than 200 mg that have excellent complexation properties [6].

Among different Cyclodextrins, beta cyclodextrin (BCD) has been the most commonly used inclusion compound owing to its vast availability, low cost, absolute biocompatibility and also wide regulative acceptance [7]. Moreover, the inner cavity of BCD is fortunately more appropriate for phytoconstituents like curcumin, and also for BCS-II synthetic drugs loading over other types of cyclodextrins [8]. Nevertheless, the poor aqueous solubility of BCD is a major hurdle in its vast application. A surge of scientific studies in this area detected that the incorporation of a small amount of suitable auxiliary materials like hydrophilic polymers, organic acids, amino acids, and hydroxyl organic amines, to a drug-BCD complex could ameliorate both the complexation and solubilizing potentialities of the BCD, and ultimately decreases its amount in pharmaceutical formulations [9, 10]. Such outcomes have been attributed to the complementary effect of added substance, and BCD to the formulation of ternary complexes.

The mechanism that participates in increasing CD complexation efficiency in the presence of added substances which are water-soluble has not yet been fully understood; however, it has been believed that the mobility of CD can be reduced, and the complex solubility can be increased by adding water-soluble polymers [11]. The addition of auxiliary substances such as water-soluble polymers has been shown to enhance the drug bioavailability, and cause an up to 80% reduction in the used amount of CD [12].

The aim of this review was to outline the influence of different types of hydrophilic compounds on drug-CD complex, and also various methods used for the formation of cyclodextrin ternary inclusion complexes. The electronic databases such as Google Scholar, E-Resource Portal of Imam Abdulrahman bin Faisal University, Scopus, PubMed, Springer Link, etc. also textbooks were used to gather all the related information about cyclodextrin ternary inclusion complexes.

INFLUENEC OF HYDROPHILIC COMPOUNDS ON DRUG COMPLEXATION WITH CYCLODEXTRINS.

Mayank and Rajashree (2018) investigated the interaction of Cinnarizine (CIN) with Hydroxypropyl-ß-Cyclodextrin (HPßCD) with the axillary substance Hydroxy Acids (HA). They prepared different binary and ternary inclusion complex of CIN with HPßCD and HA by kneading and co-evaporation methods. In the formation of ternary systems, HAs have been used in three different concentrations. The phase solubility method was used to study the interaction in the solution phas; and the Fourier Transform Infrared (FTIR) spectroscopy, Proton Nuclear Magnetic Resonance (1H-NMR), Scanning Electron Microscopy (SEM), X-Ray Diffractometry (XRD), and Differential Scanning Calorimetry (DSC) were used to study the solid phase interaction. The positive effect of HA on the complexation of CIN with HPßCD was shown by Phase solubility. In this study, for the confirmation of ternary complex formation, the solid phase studies were used. A solubility and dissolution study explained that out of three various concentrations tried, HAs were with the greatest effect at the 1 molar concentration. Ternary systems were much more effective in enhancing the solubility and dissolution profile of CIN than the CIN-HPßCD binary systems [13].

Jafar et al (2018) improved the water solubility and dissolution profile of an NSAID meloxicam by using hydroxy propyl ß-cyclodextrin ternary complexes employing co-solvents ethanolamines. First, kneading and solvent evaporation techniques were used to formulate meloxicam (MLX) binary complexes with Hydroxy propyl ß-Cyclodextrin (HPßCD), then ternary complex of selected MLX-HPßCD binary complex was formulated by employing various ethanolamines through solvent evaporation method. The solvent evaporation method was the best one in the preparation of binary complex of meloxicam at the primary stage of the study, so it was used for preparing the ternary complex as well. MLX formed 1:1 M stoichiometric binary, and ternary inclusion complexes as clarified by the AL-type of phase solubility curve. An increase in the stability constant value (Kc) of MLX- HPßCD complex when ethanolamines added, conceded the higher complexation efficiency. Solid-state analysis by FTIR, TGA, and SEM of ternary complex evidenced the perfect inclusion complex formation. Ternary complexes showed better enhancement in drug dissolution when compared to the pure MLX and MLX-HPßCD binary complex. The ternary complex containing 1:1:1 molar ratio of MLX-HPßCD-DEA showed 86.91% drug dissolution over 1 hour, which was significantly high in relation to the ternary complexes containing monoethanolamines and triethanolamines, and it was found to follow imperatively matrix order release mechanism. Previously studied complexes illustrated that there was no significant change in physical appearance, drug content or drug dissolution, which clearly showed the high in-vitro stability [14].

Merce et al (2018) in their study, investigated the spectroscopic parameters for the chelating power of supramolecular structures in the presence of Gallium and palladium, which are two important metal ions especially considered in the medical science. The obtained ternary complexes presented some degree of insolubility in many organic solvents, and different mixed proportions could be studied by a number of analytical techniques. The binding constants for the complexes in a major aqueous solution were not possible to be determined by Potentiometric Titrations, and the possible reasons were addressed. In the complexation, it was found out that based on the host in the ßCD structure and to the binded metal ion, the participating basic sites were different, which resulted in a different spatial conformation and a distortion in the 3D structure. Bragg's peak values 2 for all the binary and ternary assemblies were given. Infrared spectroscopy gave the best wavelengths for the differentiation of the metal complex. C-3 from 13 Vitamin D and of C-2, C-3 and C-6 from ßCD gave the most probable depronated –OH groups for the formation of a ternary complex. The analytical techniques of C NMR, UV-NIR and powder XRD, characterized the binary and the ternary supramolecular structures [15].

Ding et al (2018) studied the effect of a polymer hydroxypropyl methylcellulose on the complex formation of fenofibrate and hydroxypropyl-ß-cyclodextrin (HP-ß-CD). At first, they examined the phase solubility with an extra amount of drug in the HP-ß-CD solutions with and without hydroxypropyl methylcellulose (HPMC). The binary and ternary complexes were made by ball milling. Fourier changed infrared spectroscopy (FI-IR), differential scanning calorimetry (DSC), X-ray powder diffraction (XPRD) and nuclear magnetic resonance spectroscopy (1H-NMR) which were utilized for characterizing the complex. The AL type phase-solubility diagram showed that the complexes of fenofibrate and HP-ß-CD were formed with molecular ratio of 1:1. The results of the analysis confirmed the formulation of the inclusion complexes. To sum up, the interaction occurring between fenofibrate and HP-ß-CD in the complexes and the HPMC effectively improve the complexation efficiency and stability constant. The in-vitro dissolution test suggested that the releasing of fenofibrate in ternary complex was greater than binary complex [16].

Jafar et al (2017) ameliorated the rate of dissolution and the aqueous solubility of an anti-diabetic drug Glimepiride by the incorporation in ternary cyclodextrin complexes engaging amino-acids. Primarily, the binary complexes of Glimepiride GMP, ß-Cyclodextrin (ßCD) and Hydroxy propyl ß-Cyclodextrin (HPßCD) were formulated using physical mixing method, solvent evaporation kneading, and spray drying. The binary complex of GMP Cyclodextrin was incorporated with several amino-acids in order to form ternary complex via kneading method. Kneading method was selected in order to prepare ternary complexes of glimepiride, due to the proven ability in yielding binary complexes of GMP in the beginning of the study. Glimepiride formulated (1:1) M stoichiometric binary, and ternary insertion complexes as evinced in the phase of solubility curve (AL-type). A raise in kc -stability constant value- of the complex (glimepiride - ßCD/HPßCD) in company with amino-acids displayed advanced complexation capability. The optimal insertion complexes creation was demonstrated by utilizing DSC, FTIR studies. The dissolution of the drug in ternary complexes was improved in comparison with binary (GMP-ßCD) and glimepiride alone. The ternary complex was composed of a molar proportion of (1 GMP: 3 HPßCD: 2 L-ARGININE), and showed a drug dissolution of 98.85% in span of two hours, which was meaningfully greater compared to the other amino-acids' ternary complexes. In addition, it showed following the first order based on the law of Hixson-Crowell's cube root. The great in-vitro stability was displayed with the stability of the content of the drug, physical characteristics, and dissolution. [17]. There have been a lot of such reports (Table-1), wherein researchers proved the positive influence of variety of hydrophilic compounds in ameliorating the complexation and aqueous solubility potential of cyclodextrins, and reducing their bulk in pharmaceutical formulations.

AbouEllef, et al (2018) examined thermodynamic solvation parameters for saturated benzoic acid and some of its derivatives in binary mixtures of ethanol and water. The solubility was increased when the mole fraction of ethanol increased in the binary mixtures, and also their solvation behaviors were increased by increasing temperature [18].

TECHNIQUES FOR THE FORMULATION OF TERNARY INCLUSION COMPLEXES

Cyclodextrins contain inner lipophilic holes, belong to OH groups in the outer layer, and the insertion of lipophilic drugs occurred utilizing hydrophobic binding among the drug molecules with the inner hole of cyclodextrin [19]. Nevertheless, other bonds like dipole-dipole and van der Walls binding might be engaged in the binding of the guest compound. The creation of cyclodextrins has been a modest procedure despite several different factors and numerous different binding forces. Several methods can be utilized in order to obtain cyclodextrin- drug complex based on the characteristics of the guest and the selected cyclodextrin.

Spray drying method

It is a significant promising method of the preparation of cyclodextrin ternary inclusion complexes. In this method, cyclodextrin along with drug and auxiliary substances is dissolved in a common solvent, and the fluid is converted into solid particles, by atomization process by the contact of droplets with hot gaseous medium converting the droplets into dry powder with zero moisture content [20]. Four main steps engaged within spray drying method are as under: 1st: automation of the liquid feed; 2nd: drying spry into dry gas; 3rd: the formation of the dry particles; and 4th: collecting the powder.

- **Variables affecting the product of spry drying:**

The main affecting variables are the parameters of process (flow rate of liquid feed, rate of flowing of drying gas, the rate of drying, gas inlet temperature, the percentage of aspiration, type of gas, pressure). Liquid feed (including viscosity, concentration, density, surface tension, solvent point boiling), and other variables such as co-current flow, counter-current flow, mixed flow and atomizer geometry are examined [21].

- **Advantages:**

Spray drying technique compared to the other techniques has been considered fast, convenient, reproducible single step [22]. And, it has relevance to both manufacturing and research laboratory locations [23]. Moreover, in spray drying, no major final modification is needed in the final step of drying to generate particles as in the other methods such as emulsion, solvent evaporation [24]. Additionally, compared to the freeze-drying technique, spry drying is less time consuming and less costly because it does not include deep cooling, which consumes extensive energy [23]. Spray drying is suitable for heat-sensitive substances without harming the substances [25]. Other advantages of spray drying is the fast evaporation of the solvent because of the high surface area-to-volume ratio [26]. Spray drying increases the shelf-life of the products by making dry powder [27]. It is used in different areas of industry (e.g. encapsulation of drugs, aromatic oils, pigments, flavors. etc.), and in addition it is used to produce different types of carriers like microparticles, polymeric nanoparticles and nanocomposite [28].

- **Disadvantages:**

The laboratory yield is considered low (20% to 70% only) due to sticking the product on the surface of the chamber wall [29]. The inefficient separation assimilation of cyclone makes tiny particles (less than 2µm) to push through exhaust air [30]. Moreover, the nanometer particles production is limited because of the lack of enough forces of liquid atomization (pressure and centrifugal) to obtain large amounts of submicron particles [31], which makes it a remarkable drawback in manufacturing IV deliver
y system which is largely affected by size and distribution [32].

Air jet milling method

Air jet mill is a device used to grind materials mostly the hard ones by using gas in high speed through the vibrating feeder. Materials pass to the chamber of grinding, then, the particles are moved by high speed air passing over nozzle before entering the chamber of grinding. By the extreme pressure and the speed from the air, the particles become agitated because of the dual interaction of particles and the wall, this agitation results in fracture plus reducing the particles magnitude [33].

- **Variables affecting the production by Air jet milling:**

Different variables can influence the manufacture of air jet mill including the rate of feeding, the pressure of the pusher nozzle and the grinding nozzle, and the type of gas used [34]. Additionally, the particle size before and after the milling process, velocity, the nozzle type and diameter, and the angle of penetration the jet -ideally 52-60 degree, the pressure of injector can affect the manufacture of air jet mill [35].

- **Advantages:**

Air jet milling has been considered as a practical method for producing very minute particles of smaller than 40 micrometers. Additionally, the energy of air jet is based on the sound speed which is contrariwise relative to the root of the gas molecular weight, so by changing the gas, the sizes of particles and their distribution is easily manageable. Moreover, there is the low risk of contamination [35]. Air jet milling has been considered as a convenient method for laboratory scale production of hard materials [36].

- **Disadvantages:**

Air jet milling has high consumption of energy [35]. In 2010, Saleem and Smyth studied the use of air jet mill for soft materials instead of hard ones to produce 5 micrometer size particles. The investigator found that air jet milling was not effective in soft materials' production. The incorporation of freeze drying along with air jet milling helped in reducing the hardness and stretchiness thus reducing the energy required by air jet milling. Moreover, the particles after milling are not used in pharmaceutical dosage directly, but considered as a transition state. Most of the times, fillers are used along with milled drugs like: (lactose, calcium phosphate) and others to overcome the problem of low flow and cohesiveness due to the high surface energy. Due to the high energy, the particles complex with the thinner diffusion boundary layer [37]. The roughness of milled drug is changed which can affect the process of wetting

[38]. Additionally, external air compressors are required to insure the high-pressure flow rate around 10 bars.

Ball milling technique

Ball mill technique is used in laboratory setting to produce micro-particles. It consists of a vessel that is occupied with balls made of diverse materials (e.g. silicon nitride, ceramic, sintered corundum, chromes steel, plastic polyamide etc.). The materials fill the vessel, then the vessel rotate and vibrate in different speed and frequency. The balls move in a pattern with each other, and they crash with the opposite wall. The forces generated from crashing the particles of the materials reduce the size [39].

- **Variables affecting the production:**

Diverse variables will influence the production including the extent of filling, and the strength of the procedure which is determined by the starting materials and the amounts of balls. Generating minute particles is influenced greatly by the compression, impaction and lengthier processing periods. Other variables including the rotation and vibration speed, density, size and hardness of balls are also affected [40].

Advantages:

Ball milling is a remarkable method used to boost the solubility of low soluble drugs. Additionally, it is used as mixing method increasing the co-ground amorphous drugs with hydrophilic excipient at the molecular level, and enhancing the dissolution and bioavailability by amorphization [41], and additionally, easing the creation of complexes [42]. The integration of excipients might reduce the milling-induced amorphization and structural abnormalizes of some substances [43]. Also, the creation of stable co-amorphous mixture of the dual drugs is classified in BCS class II [44]. In 2010, Imran et al investigated the use of air jet mill and micro-ball milling in micro-sizing of a soft substance of the ball milling found to be superior under cold condition in yielding lower range of particle size [34].

- **Disadvantages:**

Despite the effectiveness of ball milling, it is less efficient in large scale production. Jacketing is required for heat elimination and cooling the milling chamber.

Solvent evaporation method

For the formation of insertion complex, the components are dissolved in a required amount of solvent by using bath sonicator for 5 minutes, and then the solution is placed in rotary vacuum evaporator at temperature of 60°C till the solvent evaporates. The product is dried at 50°C, and stayed in the vacuum for one day, after 24 hours, the product is passed over an 80-net filter [13]. There are many factors to be considered which affect the efficacy of the encapsulation including carbon-based solvent and its amount, the rate of solvent removal, drug solubility, distribution coefficient plus molar mass of drugs [45].

- **Advantages:**

Simple procedure, ease of scale-up, less residual solvent retains the activity of bioactive compounds. It is beneficent over the melting method by producing quick and complete dissolution deprived of rebound consequences due to the higher permeable medication delivery system [46]. It prevents the presence of drug in crystalline form. It is alternative to spray drying method [47].

- **Disadvantages:**

There is a low drug-loading efficiency [48]. Oil/water emulsion followed by solvent evaporation has poor encapsulation. The efficiency of the moderately water soluble compound is not very strong to prevent the crystalline formation as compared to the spray drying method; so, the spray drying method has better dissolution profile [49].

Freeze drying / Lyophilization technique

In order to get a permeable, shapeless (amorphous) powder with the great percent of binding between drug & CD, lyophilization/freeze drying technique is considered as suitable. For the formation of insertion complex, the mandatory quantity of drug is dissolved in a required amount of solution in Stoppard vials, then, the mixture sonicates for 30 minutes after that, it is placed in an incubator shaker at 40 C for 72 hours. Then, the mixture is filtered and freeze dried. There are many factors to be considered during the formation of insertion complex such as, the length of lyophilization for each product, the exhibited external surface of the thermal currant exchange, cooling velocity, the heat transfer quality, the erosion resistance of the material spoiled with interaction with foodstuff, the metal surfaces' status in interaction with the product, and the volume of the vacuum of the lyophilization space [50].

- **Advantages:**

It is ideal for thermo-labile compounds, because it needs low temperature [51]. Associated with more significant changes in the properties of solid complexes, more effective formation of inclusion complexes is ensured [52]. An excellent yield of insertion complex is produced plus its appropriateness for the extensive production. It can be considered as a substitute method for the solvent evaporation technique because of the complete conversion of the crystalline form to the amorphous form.

- **Disadvantages:**

The charges for freeze-drying are about 5 times higher than the classical drying procedures [53]. In case of inappropriate packing and storage, the product can become wet because of the humidity which allows for the microbial growth.

Kneading method

For the formation of insertion complex, the required quantities of components dry in mortar for 15 minutes. Then the mixture is kneaded with ethanol for 45 minutes, during this process solvent can be added to reach the suitable consistency for kneading. After that, it should be dried at 50°C and stay in vacuum for one day, and then sieved through 80 net filters [54]. There are many factors which influence the formation and efficacy of inclusion complex which include the composition of powder, initial water content, and molar ratio.

- **Advantages:**

It has a simple and cheap procedure. It can be used for poor water-soluble compounds, since the compounds dissolve slowly by forming inclusion complexes. It is most widely used for essential oils encapsulation, because there is no need for high temperatures.

- **Disadvantages:**

Less quantity of medication is released as compared to the solvent evaporation method. There is not very strong prevention of crystalline formation as compared to the spray drying method, so that spray drying method has better dissolution profile. It is not suitable for the extensive production.

Different methods employed in the formulation of cyclodextrin ternary inclusion complexes which are reported in the literature as presented in Table 1.

CONCLUSION

Cyclodextrins are able to boost and ameliorate the solubility of low soluble medications, through the process of encapsulation of organic drugs in their holes; so the formation of inclusion complexes change the physical and the chemical properties of such medications. The drug:CD:Hydrophilic substances ternary complex represents an attractive substitute, particularly in situation where huge amounts of cyclodextrins is required in order to form complex, that leads to the meaningfully enlarged bulk of dosage forms. Thus, it is more likely to obtain drug delivery systems with an optimized dissolution profile, resulting in improved bioavailability.

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Table 1: Some examples of recent studies that used different hydrophilic compounds/auxiliary substances and different methods of preparation in drug-CD inclusion complexes

#	Drug	Type of cyclodextrin	Auxiliary Substances	Method(s) of preparation	References
1	Rilpivrine	β-CD, HP- β-CD	Tocopherol polyethylene glycol succinate	Solvent evaporation.	**[54]**
2	Fenofibrate	HP- β-CD	Hydroxypropyl methylcellulose	Ball-milling	**[16]**
3	Cinnarizine	HP- β-CD	Hydroxy acids	Kneading and evaporation methods.	**[13]**
4	Sulfamethoxazole	β-CD, HP- β-CD	Arginine and cysteine	Freeze drying method	**[55]**
5	Efavirenz	Hp-β-CD	L-arginine	Spray drying method.	**[56]**
6	Celecoxib	αCD, βCD, γCD, 2-hydroxypropyl β-cyclodextrin and RMβCD	HPMC, chitosan, hyaluronic acid	freeze drying method	**[57]**
7	Benznidazole	βCD	TEA, NMP	Spray-dried particles	**[58]**
8	Porphyrin	HP-β-CD, M-β-CD,Hk-β-CD	Poloxamer	Solvent evaporation method.	**[59]**
9	Nateglinide	HP-β-CD	L-arginine	kneading,Co-evaporation, and spray drying methods.	**[60]**
10	Etodolac	HP-β-CD	L-arginine	Co-evaporation, and spray drying methods	**[61]**
11	Oxaprozin	RAMEB	L-arginine and sepiolitenanoclay	Cogrinding, coevaporation, cofusion.	**[62]**
12	Ciprofloxacin	βCD, β-glycerophosphate	hexamethylenediisocyanate (HDI)	Kneading method	**[63]**
13	Oxaprozin	rameβCD	L-arginine	co-grinding, evaporation, kneading techniques.	**[64]**
14	Benznidazole	HP-β-CD	TEA, NMP	spray drying method.	**[65]**
15	Silymarin	β-CD	Sodium carboxymethyl cellulose	Kneading method.	**[66]**
16	Praziquantel	β-CD	HPMC	Kneading method freeze drying	**[52]**

				method.	
17	Telmisartan	γCD	HPMC	Freeze drying method	**[67]**
18	Ezetimibe	HP-β-CD	TPGS, AA2G	Freeze drying method.	**[68]**
19	Modafinil	HP-β-CD	TMC, PVP K30	Freeze drying method	**[69]**
20	Pimozide	β-CD	PVP-K30	Kneading method	**[70]**

REFERENCES

[1] Fauzi1,N.F.A. Abu Bakar,N.H. Mohamad,N. Hadzrullathfi,H. Omar,S. Ismail, M.Z.Thoarlim,A. Mustafa1,N.S. Nigella sativa Effects on Neurotransmitter Systems: Potential Treatment for Drug Tolerance and Dependence. International Journal of Pharmaceutical Research & Allied Sciences, 2018, 7(1):196-200.

[2] Grant N Zhang, H, 2011. Poorly water-soluble drug nanoparticles via an emulsion-freeze-drying approach. J. Colloid Interf. Sci., 356, pp. 573-578.

[3] Tsai, Y. Tsai, H. Wu, C. Tsai, F, 2010. Preparation, characterisation and activity of the inclusion complex of paeonol with β-cyclodextrin. Food Chem, 120, pp. 837- 841.

[4] Garnero, C, Zoppi, A, Genovese, D Longi, M, 2010. Studies on trimethoprim: hydroxypropyl-β-cyclodextrin: aggregate and complex formulation. Carboyd. Res., 345, pp.2550-2556.

[5] Loftsson, T.; Brewster, M, 1997. Cyclodextrins as pharmaceutical excipients. Pharm. Tech., 5, pp.26-34.

[6] Loftsson, T.; Brewster, M. E, 1996. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. J. Pharm. Sci., 85, pp.1017-1025.

[7] Mohammed Jafar, Mohammed Salahuddin, Tarek S Kayed, Niyaz Ahmad, Huda A Al-Eid, Abdullah H Al-Qarross, 2017. Buoyant in situ gels of meloxicam-β-cyclodextrin-triethanolamine ternary complex for oral delivery; from a Box-Behnken experimental design to in vivo activity detail. Asian Journal of Chemistry, 29(6), pp.1275-1284.

[8] Vivek RY, Sarasija S, Kshama D, Seema Y, 2009. Effect of cyclodextrin complexation of curcumin on its solubility and antiangiogenic and anti-inflammatory activity in rat colitis model. AAPS Pharm Sci Tech, 10(3), pp. 752–762.

[9] Folch-Cano C, Yazdani-Pedram M, Olea-Azar C, 2014. Inclusion and Functionalization of Polymers with Cyclodextrins: Current Applications and Future Prospects. Molecules, 19, pp.14066-14079.

[10] Jafar M, Salahuddin M, Bolla SR, 2018. Gastric floating in-situ gel as a strategy for improving anti-inflammatory activity of meloxicam. J App Pharm Sci, 8(11), pp. 095–102.

[11] Veiga, F. Pecorelli, C. Ribeiro, L, 2006. As ciclodextrinasemtecnologiafarmacêutica. Coimbra: Minerva Coimbra. pp. 9-33.

[12] Mura, P.; Faucci, M.T.; Bettinetti, G.P, 2001. The influence of polyvivylpyrrolidone on naproxen complexation with hydroxypropyl-β-cyclodextrin. Eur. J. Pharm. Sci.,13, pp.187-194.

[13] Mayank Patel, Rajashree Hirlekar, 2018. Multicomponent cyclodextrin system for improvement of solubility and dissolution rate of poorly water soluble drug. Asian Journal of Pharmaceutical Sciences, https://doi.org/10.1016/j.ajps.2018.02.007.

[14] Jafar M, Salahuddin M, Kayed TS, Ahmad N, Al-Eid HA, Al-Qarross AH, 2018. Solid state analysis and in-vitro dissolution behavior of meloxicam-hydroxy propyl beta cyclodextrin-ethanolamines ternary complexes. Int J Pharm Qual Assurance, 9(1), pp. 80–6.

[15] Ana Lucia Ramalho Mercê, Jamal Rafique, Bruno Szpoganicz, 2018. Synthesis and structural characterization of gallium (iii) and palladium (ii) on the formation of ternary supramolecular assemblies. Part 1: β -cyclodextrin – cholecalciferol. International Journal of Scientific Research, 7(2), pp.1-6.

[16] Ding, X., Zheng, M., Lu, J. Zhu, X., 2018. Preparation and evaluation of binary and ternary inclusion complexes of fenofibrate/hydroxypropyl-β-cyclodextrin. J Incl Phenom Macrocycl Chem, 91, pp. 17-24.

[17] Mohammed Jafar, Ashok Malpani, Mohammed Imran Khan, 2017. Ameliorated solubility and dissolution rate of glimepiride by cyclodextrin ternary complexes employing amino acids. International Journal of Pharmaceutical Sciences and Research, 8(6), pp. 2443-2451.

[18] AbouEllef, E.M. Gomaa, E.A.& Mashaly,M.S. Thermodynamic Solvation Parameters for Saturated Benzoic Acid and some of its Derivatives in Binary Mixtures of Ethanol and Water. J Biochem Tech (2018) 9(2): 42-47.

[19] Hedges AR, Shieh WJ, Sikorski CT, 1995. Use of cyclodextrins for encapsulation in the use and treatment of food products. In: Risch, S.J. and

Reineccius, G.A. (Eds). Encapsulation and controlled release of food ingredients. American Chemical Society, Washington, DC. Pp. 60-73.

[20] Jonathan J. O'Sullivan, Eve-Anne Norwooda, James A. O'Mahonya, Alan L. Kelly, 2019. Atomisation technologies used in spray drying in the dairy industry: A review. Journal of Food Engineering, 243, pp.57–69

[21] Alejandro Sosnik, Katia P. Seremeta, 2015. Advantages and challenges of the spray-drying technology for the production of pure drug particles and drug-loaded polymeric carriers. Advances in Colloid and Interface Science, 223, pp. 40–54.

[22] Wan F, Bohr A, Maltesen MJ, Bjerregaard S, Foged C, Rantanen J, et al, 2013. Critical solvent properties affecting the particle formation process and characteristics of celecoxib-loaded PLGA microparticles via spray-drying. Pharm Res , 30, pp. 1065–76.

[23] Gong P, Zhang L, Han X, Shigwedha N, Song W, Yi H, et al, 2014. Injury mechanisms of lactic acid bacteria starter cultures during spray drying: a review. Dry Technol, 32, pp. 793–800

[24] Baras B, Benoit MA, Gillard J, 2000. Parameters influencing the antigen release from spray-dried poly (DL-lactide) microparticles. Int J Pharm, 200(1). pp.133–45.

[25] Anish C, Upadhyay AK, Sehgal D, Panda AK, 2014. Influences of process and formulation parameters on powder flow properties and immunogenicity of spray dried polymer particles entrapping recombinant pneumococcal surface protein A. Int J Pharm, 466, pp. 198–210

[26] Fatnassi M, Tourné-Péteilh C, Peralta P, Cacciaguerra T, Dieudonné P, Devoisselle JM, et al, 2013. Encapsulation of complementary model drugs in spray-dried nanostructured materials. J Sol-Gel SciTechnol, 68, pp. 307–16.

[27] Gharsallaoui A, Roudaut G, Chambin O, Voilley A, Saurel R, 2007. Applications of spraydrying in microencapsulation of food ingredients: an overview. Food Res Int. 40, pp.1107–21.

[28] Tewa-Tagne P, Briançon S, Fessi H, 2007. Preparation of redispersible dry nanocapsules by means of spray-drying: development and characterisation. Eur J Pharm Sci, 30, pp. 124–35

[29] Rabbani NR, Seville PC, 2005. The influence of formulation components on the aerosolisation properties of spray-dried powders. J Control Release, 110, pp.130–40.

[30] StåhlK, Claesson M, Lilliehorn P, Lindén H, Bäckström K, 2002. The effect of process variables on the degradation and physical properties of spray dried insulin intended for inhalation. Int J Pharm, 233, pp. 227–37.

[31] Maury M, Murphy K, Kumar S, Shi L, Lee G, 2005. Effects of process variables on the powder yield of spray-dried trehalose on a laboratory spray-dryer. Eur J Pharm Biopharm, 59, pp. 565–73

[32] ElmowafyE, Osman R, El-Shamy AH, Awad GA, 2014. Nanocomplexes of an insulinotropic drug: optimization, microparticle formation, and antidiabetic activity in rats. Int J Nanomedicine, 9, pp. 4449–65.

[33] Tanaka T, Kanda Y. Crushing and grinding. In: Masuda H, Higashitani K, Yoshida H, 2006. Powder technology handbook. 3. New York: CRC Taylor and Francis

[34] Imran Y. Saleem, Hugh D. C. Smyth, 2010. Micronization of a Soft Material: Air-Jet and Micro-Ball Milling. AAPS Pharm SciTech, 11(4), pp. 1642–1649

[35] Alain Chamayou, John A. Dodds. 2007. Chapter 8 Air Jet Milling. Handbook of Powder Technology, 12, pp. 421-435

[36] Vatsaraj BN, Gao D, Kowalski LD, 2003. Optimization of the operating conditions of a lab scale aljet mill using lactose and sucrose: a technical note. AAPS PharmSciTech, 4(2):p. Article 27.

[37] Bisrat M, Nystrom C, 1988. Physicochemical aspects of drug release. Viii. The relation between particle size and surface specific dissolution rate in agitated suspensions. Int J Pharm, 47, pp. 223-231.

[38] Ho R, Dilworth SE, Williams DR, 2011. Role of surface chemistry and energetics in high shear wet granulation. IndEngChem Res, 50, pp. 9642-9649.

[39] Colombo I, Grassi G, Grassi M, 2009. Drug mechano-chemical activation. J Pharm Sci, 98, pp. 3961-3986.

[40] Zhi Hui Loh, Asim Kumar Samanta, Paul Wan SiaHeng, 2015. Overview of milling techniques for improving the solubility of poorly water-soluble drugs. Asian journal of pharmaceutical sciences, 10, pp. 255- 274.

[41] Yamamoto K, Nakano M, Arita T, 1974. Dissolution rate and bioavailability of griseofulvin from a ground mixture with microcrystalline cellulose. J Pharmacokinetic Biopharm, 2, pp. 487-493.

[42] Mallick S, Pattnaik S, Swain K, et al. 2008. Physicochemical characterization of interaction of ibuprofen by solid-state milling with aluminum hydroxide. Drug Dev Ind Pharm, 34, pp. 726-734.

[43] Balani PN, Ng WK, Tan RB, et al. 2010. Influence of excipients in comilling on mitigating milling-

induced amorphization or structural disorder of crystalline pharmaceutical actives. J Pharm Sci, 99, pp. 2462-2474.

[44] Lobmann K, Strachan C, Grohganz H, et al. 2012. Co-amorphous simvastatin and glipizide combinations show improved physical stability without evidence of intermolecular interactions. Eur J Pharm Biopharm, 81, pp. 159-169.

[45] Shashank Tiwari and PreranaVerma, 2011. Microencapsulation technique by solvent evaporation method (Study of effect of process variables). Int. J. of Pharm. & Life Sci, 2, 8. 998-1005

[46] F. Bouchala, B, M. Skiba A, N. Chaffai C, F. Hallouard A, S. Fatmi B, M. Lahiani-Skiba, 2015. Fast dissolving cyclodextrin complex of piroxicam in solid dispersion Part I: Influence of b-CD and HPb-CD on the dissolution rate of piroxicam. International Journal of Pharmaceutics, 478, pp.625–632.

[47] Patil J.S., Kadam D.V., Marapur S.C., KamalapurM.V, 2010. Inclusion complex system; a novel technique to improve the solubility and bioavailability of poorly soluble drugs: a review. Int J Pharmaceutical Sci Reivew & Res. 2010; 2(2):29-34.

[48] Wi Hyoung Lee, DonghoonKwak, John E. Anthony, Hwa Sung Lee, Hyun Ho Choi, Do Hwan Kim, Seung Goo Lee, Kilwon Cho, 2012. The Influence of the Solvent Evaporation Rate on the Phase Separation and Electrical Performances of Soluble Acene-Polymer Blend Semiconductors. Advanced Functional Matters, 22, 2. https://doi.org/10.1002/adfm.201101159

[49] Vasanti Suvarna, Apeksha Kajwe, Manikanta Murahari, Gurubasavaraj V. Pujar, Bharath Kumar Inturi, Atul P. Sherje, 2017. Inclusion Complexes of Nateglinide with HP–β–CD and L-Arginine for Solubility and Dissolution Enhancement: Preparation, Characterization, and Molecular Docking Study. J Pharm Innov, 12, pp. 168–181.

[50] Dumitru Mnerie, Gabriela Victoria Anghel, AlinVasileMnerie, Constantin Cheveresan, 2007. A comparison of Factors that Influence the Lyophilization Process. Agriculturae Conspectus Scientificus, 72 (4), pp. 367-370.

[51] Necla Ozdemira, Cícero C. Polab, Bruna N. Teixeirac, Laura E. Hilld, Ali Bayraka, Carmen L. Gomesd, 2018. Preparation of black pepper oleoresin inclusion complexes based on beta-cyclodextrin for antioxidant and antimicrobial delivery applications using kneading and freeze drying methods: A comparative study. LWT - Food Science and Technology, 91, pp. 439–445.

[52] Layany Carolyny da Silva Moura˜o, Daiane Rafaela M. Ribeiro Batista, Sara Braga Honorato, Alejandro Pedro Ayala, Waldenice de AlencarMorais, Euze´bio Guimara˜es Barbosa, Fernanda Nervo Raffin, Tu´lio Fla´vioAccioly de Lima e Moura, 2016. Effect of hydroxypropyl methylcellulose on beta cyclodextrin complexation of praziquantel in solution and in solid state. J Incl Phenom MacrocyclChem, 85, pp. 151–160.

[53] Cristina R, 2001. Hot air and freeze-drying of high-value foods: a review, Journal of Food Engineering, 49, pp. 311–319.

[54] Monica R. P. Rao, JagrutiChaudhari, Francesco Trotta, and Fabrizio Caldera, 2018. Investigation of cyclodextrin-based Nanosponges for solubility and bioavilability enhancement of Rilpivirine. AAPS PharmSciTech, 19(5). DOI: 10.1208/s12249-018-1064-6

[55] Beena Varghese, FakhrEldin O. Suliman, Aalia Al-Hajri, NahedSurur S Al Bishri, Nathir Al-Rwashda, 2018. Spectral and theoretical study on complexation of sulfamethoxazole with B- and HPB- cyclodextins in binary and ternary systems. Spectrochimica Act a part A: molecular and biomolecular spectroscopy, 190, pp. 392-401

[56] Vasanti SuvarnaA, SiddhataThorat A, Usha Nayakb, AtulSherje A, Manikanta Murahari, 2018. Host-guest interaction study of Efavirenzwithhydroxypropyl-β-cyclodextrin and L-arginine by computationalsimulation studies: Preparationand characterization ofsupramolecular complexes. Journal of Molecular Liquids, 259, pp. 55–64.

[57] Phatsawee Jansook, Pakin Kulsirachote, Thorsteinn Loftsson, 2018. Cyclodextrinsolubilization of celecoxib: solid and solution state characterization. Journal of inclusion phenomena and macrocyclic chemistry, 90, pp. 75-55.

[58] Polyanne N. de Melo, Lilia B. de Caland, Matheus F. Fernandes-Pedrosa, Arno´bio Anto^nio da Silva-Ju´ Nior, 2018. Designing and monitoring microstructural propertiesof oligosaccharide/co-solvent ternary complex particles to improve benznidazole dissolution. J Mater Sci, 53, pp. 2472–2483.

[59] Victoria J. Valeron Bergh, Hanne Hjorthtonnesen, 2017. Interaction and solubilization of 5, 10, 15, 20-tetrakis (4-hydroxyphenyl) porphyrin with poloxamer 407 and B-cyclodextrin-derivatives in binary and ternary systems. Journal of drug delivery and technology, 37, pp. 51-60.

[60] Vasanti Suvarna, Apeksha Kajwe, ManikantaMurahari, GurubasavarajV.Pujar,

Bharath Kumar Inturi, Atul P. sherje, 2017. Inclusion complex of Nateglinide with HP-B-CD and L-arginine for solubility and dissolution enhancement: preparation, characterization, and molecular docking stugy. J pharm Innov, 12, pp. 168-181.

[61] Atul P. Sherje, Vaidehi Kulkarni, ManikantaMurahari, Usha Y. Nayak, Pritesh Bhat, Vasanti Suvarna, and Bhushan Dravyakar, 2017. Inclusion complexation of Etodolac with hydroxypropyl-beta-cyclodextrin and auxiliary agent: formulation characterization and molecular modeling studies.mol. Pharmaceutics, 14, pp. 1231-1242.

[62] Francesca Maestrelli, Paola Mura, Marzia Cirri, NatasciaMennini, Carla Ghelardini, Lorenzo Di Cesare Mannelli, 2017. Development and characterization of fast dissolving tablets of oxaprozin based on hybrid systems of the drug with cyclodextrins and nanoclays. International journal of pharmaceutics, 531, pp. 640-649.

[63] Mirna Pereira Moreiraa, George Ricardo Santana Andradea, Marcia Valeria Gaspar de Araujob, Tatiana Kubotab, Iara F. Gimeneza, 2016. Ternary cyclodextrin polyurethanes containing phosphate groups:Synthesis and complexation of ciprofloxacin. Carbohydrate Polymers, 151, 557–564.

[64] Natascia Mennini, Francesca Maestrelli, Marzia Cirri, Paola Mura, 2016. Analysis of physicochemical properties of ternary systems ofoxaprozin with randomly methylated-ß-cyclodextrin and l-arginineaimed to improve the drug solubility. Journal of Pharmaceutical and Biomedical Analysis, 129, 350–358

[65] Polyanne N. de Melo A, Euzébio G. Barbosa A, Claudia Garnero B, Lilia B. de CalandA, Matheus F. Fernandes-Pedrosa A, Marcela R. Longhi b, ArnóbioAntônio da Silva-Júnior, 2016. Interaction pathways of specific co-solvents withhydroxypropyl-β-cyclodextrin inclusion complexes with benznidazolein liquid and solid phase. Journal of Molecular Liquids, 223, pp. 350–359.

[66] Mohammad Javed Ansari, 2016. Formulation and physicochemical characterization of sodium carboxy methyl cellulose and β cyclodextrin mediated ternary inclusion complexes of silymarin. IJPSR 7(3), pp. 984-990.

[67] Chutimon Muankaew, PhatsaweeJansook, HákonHrafnSigurpsson, Thorsteinn Loftsson, 2016. Cyclodextrin-based telmisartan ophthalmic suspension: Formulation development for water-insoluble drugs. International Journal of Pharmaceutics, 507, pp. 21–31.

[68] Kale Mohana Raghava Srivalli, Brahmeshwar Mishra, 2016. Improved Aqueous Solubility and AntihypercholesterolemicActivityof Ezetimibe on Formulating with Hydroxypropyl-β-Cyclodextrinand Hydrophilic Auxiliary Substances. AAPS PharmSciTech, 17(2), pp. 272-283.

[69] Parth Patel, Y.K. Agrawal, Jayrajsinh Sarvaiya, 2016. Cyclodextrin based ternary system of modafinil: Effect of trimethylchitosan and polyvinylpyrrolidone as complexing agents. International Journal of Biological Macromolecules,84, pp.182–188

[70] Hriday Bera, Swathi Chekuri, Srimanta Sarkar, Sanoj Kumar, Nagendra BabuMuvva, SrilathaMothe, Jhansirani Nadimpalli, 2016. Novel pimozide-β-cyclodextrin-polyvinylpyrrolidone inclusion complexes for Tourette syndrome treatment. Journal of Molecular Liquids, 215, pp.135-143.