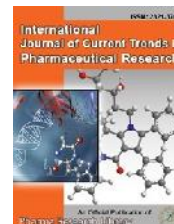




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Review Article

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## Pharmaceutical Cocrystals: An Emerging New Class of Solid Dosage Forms with Improved Physicochemical Properties

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### ABSTRACT

The increasing frequency of drugs which have poor aqueous solubility, manufacturability and stability in development offers risk of new drug products with low and variable bioavailability particularly for those drugs administered by the oral route, with consequences for safety and efficacy. Although number of strategies exists for enhancing the bioavailability of these drugs, newer strategies, dependent on the physical and chemical nature of the molecules are being developed. Crystal engineering approach presents a number of routes such as co-crystallization, polymorphism and salt formation to improve physicochemical properties of drugs, which can be implemented through a detailed knowledge of crystallization processes and the molecular properties of drugs. Pharmaceutical co-crystals are emerging as a new class of solid drugs with improved physicochemical properties, which has attracted increased interests from both industrial and academic researchers. In the present review, the concept of co-crystallization to improve solubility of drug molecules has been discussed.

**Keywords:** oral route, Pharmaceutical co-crystals, chemical nature, stability

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## 1. Introduction

Solubility is the property of a solid, liquid, or gaseous chemical substance called *solute* to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution<sup>1</sup>. The solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. The extent of solubility ranges widely, from infinitely soluble (fully miscible) such as ethanol in water, to poorly soluble, such as silver chloride in water. The term *insoluble* is often applied to poorly or very poorly soluble compounds<sup>2</sup>. Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g., precipitation of solids). Solubility equilibrium occurs when the two processes proceed at a constant rate. Under certain conditions equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable<sup>3</sup>. Combinatorial chemistry and high-throughput screening used in drug discovery have resulted in an increase of poorly water soluble drug candidates<sup>6</sup>. Currently, approximately 40% of the marketed immediate release (IR) oral drugs are categorized as practically insoluble (<100 g/mL)<sup>7</sup>. The aqueous solubility of a drug is a critical determinant of its dissolution rate. The limited dissolution rate arising from low solubility frequently results in the low bioavailability of orally administered drugs, and compounds with aqueous solubility lower than 100 g/mL generally present dissolution-limited absorption<sup>8</sup>. Common problems that challenge the successful drug delivery and manufacture of a drug molecule include deficiencies in their properties, such as solubility, stability, bioavailability, organoleptic properties and mechanical properties. Now a day the most challenging situation is to enhance solubility of certain drugs. Co-crystallization is an effective crystal engineering approach to improve various properties of the drug as well as modifying crystal structure. Co-crystals basically consists of two components that are the API and the former. “Cocrystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through noncovalent interactions, primarily hydrogen bonding”<sup>14</sup>. The formation of a pharmaceutical cocrystal involves incorporation of an API with a pharmaceutically acceptable molecule in the crystal lattice. The resulting multicomponent crystalline phase maintains the intrinsic activity of the parent API<sup>15</sup>. A more refined definition of a co-crystal can be “multicomponent crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is an acceptable molecule or ion”. Some drugs marketed in the form of racemic co crystals include: atenolol, atropine, certirazine, disopyramide, fluoxetine, ketoprofen, loratadine, modafinil, omeprazole, warfare and zopiclone. Pharmaceutical co-crystals are non-ionic supramolecular complexes and can be used to address physical property issues such as solubility,

stability and bioavailability in pharmaceutical development without changing the chemical composition of the API. This complex can be formed by several types of interaction, including pi-stacking, hydrogen bonding, and van der Waals forces. For nonionizable compounds co-crystals enhance pharmaceutical properties by modification of chemical stability, mechanical behaviour, moisture uptake, solubility, dissolution rate and bioavailability<sup>9,10</sup>. Of them we would like to mention structural modification of the molecules (to decrease the energy of crystal lattice) and preparation of pharmaceutical cocrystals. Pharmaceutical cocrystallization is emerging as an attractive alternative to polymorphs, salts and solvates in the modification of an active pharmaceutical ingredient (API) during dosage form design. The intellectual property implications of creating cocrystals are also highly relevant. This approach of co-crystal involves the expansion of a supramolecular library of co-crystallizing agents. A hierarchy of guest functional groups is classified within the library according to a specific role to a crystal packing arrangement, which is dependent on the host molecule functionalities. These are obtained from investigation of structure property relationships present in the Cambridge Structural Database(CSD) which contains classes of known crystal structures<sup>12</sup>. Recent years have witnessed a rapid growth of interest in the design and synthesis of multi-component crystals in the context of pharmaceutical cocrystal<sup>13</sup>. Cocrystal former employed in cocrystallization may be an excipient or another drug<sup>16</sup>. A number of pharmaceutical cocrystals have been reported to date with cocrystal formers selected from the list of GRAS (generally recognized as safe) compounds which includes various food additives, preservatives and pharmaceutical excipients<sup>17</sup>. **Formulation development based on biopharmaceutics classification system: [Biopharmaceutics classification system]:** The Biopharmaceutical Classification System (BCS) is an experimental model that measures permeability and solubility under prescribed conditions. The Biopharmaceutical Classification System (BCS) is an available developed guidance proposed by Prof. G. L. Amidon to predict the gastrointestinal drug absorption based on solubility and permeability of drugs<sup>21,22</sup>. This guidance may be also used to establish the correlation between in vitro dissolution and in vivo bioavailability of drug products in early drug development<sup>23,24</sup>. Currently only 8% of new drug candidates have both high solubility and high permeability<sup>25</sup>. More than 40–60% of commercially available active pharmaceutical ingredients (APIs) have been reported to have poor water solubility problems, leading to the limitation of their efficacy<sup>26</sup>. Therefore, how to enhance the solubility of APIs should be the crucial problem in the developing performance of various drug dosage forms. The bioavailability of drug is characterized by two key parameters: solubility and membrane permeability based on these two parameters, Amidon et al. proposed the so-called biopharmaceutical drug classification system (Fig. 1). According to this system, all drugs can be arbitrarily divided into four classes in terms of their potential applicability<sup>27</sup>.

According to the BCS system, APIs are categorized into four categories:

- (1) High permeability, high solubility;
- (2) High permeability, low solubility;
- (3) Permeability, high solubility and
- (4) Low permeability, low solubility

A drug substance is considered highly soluble when the highest dose strength is soluble in  $\leq 250$  ml water over a pH range of 1 to 7.5 and highly permeable when the extent of absorption in humans is determined to be  $\geq 90\%$  of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.

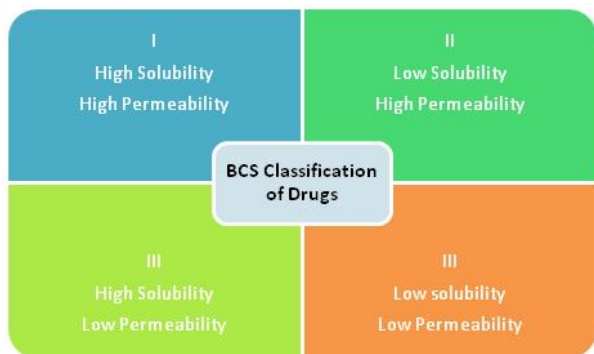


Figure1: BCS Classification of drugs

**Class I** drugs exhibit high solubility and permeability, they hold a great promise for application.

**Class II** drugs, too, have certain perspectives, provided their solubility parameters are corrected. The following approaches to solubility correction have been reported: preparation of salts<sup>28</sup>. Reduction of particle size<sup>29</sup>, introduction of nucleation inhibitors<sup>30</sup>, design of metastable polymorphous modifications synthesis of solid dispersions<sup>33</sup> complex formation, and cocrystal<sup>35,36</sup> and lipid technologies<sup>37</sup>.

**Class III** drugs require correction of membrane permeability (synthetic stage of structural correction). This problem is usually solved by using prodrugs<sup>38</sup>, locomotive molecules which ensure drug permeation through membrane<sup>39</sup>, etc.

**Class IV** drugs cannot be applied without special delivery systems. As a rule, their oral formulations are completely inefficient, and, therefore, alternative administration routes, for example, intravenous, should be used. About 40% of drugs marketed in European countries, USA, and Japan are almost insoluble in aqueous media<sup>40</sup>.

Table1: Distribution of drug classes on the market and under development

Drug class	Solubility	Permeability	Shares of drugs, %	
			On the market	Under development
I	High	High	35	5-10
II	Low	High	30	60-70
III	High	Low	25	5-10
IV	Low	Low	10	10-20

Table 1 shows the shares of marketed drugs and drugs that are under trials/development in pharmaceutical companies<sup>41</sup>. Class II is the most abundant (30% marketed drugs and 60–70% drugs under development). Just this class attracts the greatest attention of many pharmaceutical companies, since the solubility correction of drugs that have passed pre- and clinical trial cycles does not require essential financial investments and time consumption for the product to be launched on market.

**Crystal formulation in pharmaceutical sciences:** The selection of crystal form is a critical step in pharmaceutical development. Indeed, crystallization is generally used as a separation or purification method in the production of substances due to its high stability and ease in processing. The vast majority of active pharmaceutical ingredients (APIs) are isolated in the solid form and the selection of crystal form is invariably considered to be the first step in formulation development (Fig. 2.).



Figure 2: Steps in the selection of crystal form in the development of the API.

The ubiquitous nature of APIs i.e. they contain multiple hydrogen bonding sites makes them inherently predisposed to form multiple crystal forms. These crystal forms include but are not limited to salts, hydrates, solvates, polymorphs and pharmaceutical cocrystals<sup>42</sup> (Fig.3).

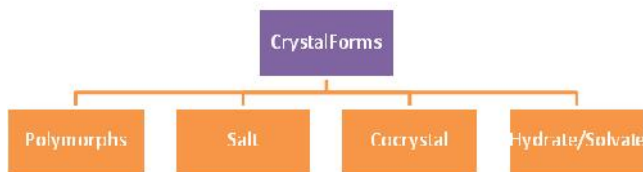


Figure 3: Schematic representation of the types of crystal forms exhibited by APIs.

As bioavailability is a function of solubility, poor oral bioavailability has become characteristic of many new drug candidates<sup>43,44</sup>. In fact, drug candidates with poor bioavailability are the primary reason why 41% of new drug candidates fail in preclinical and clinical development and 90% of new drug candidates fall into BCS class II and class IV (Figure 4).<sup>45,46</sup>

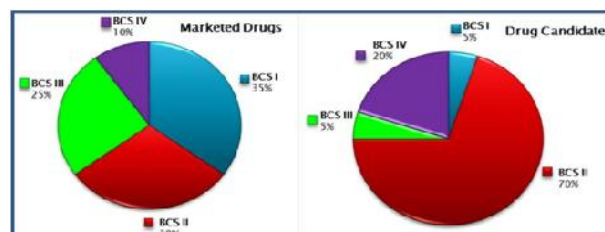


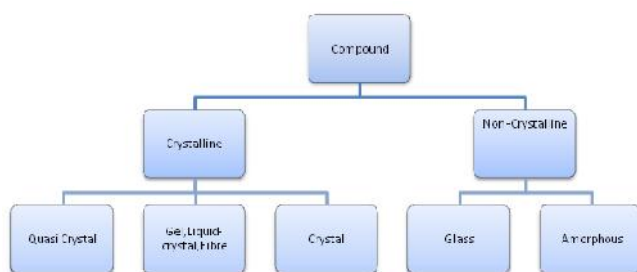
Figure 4: Comparison of BCS classification of marketed drugs and new drug candidates.

**Classification of Cocrystal:** The following classification has been proposed by the FDA: Co-crystals should be

classified within the Agency's current regulatory framework as dissociable "API-excipient" molecular complexes. They may then be treated as a "drug product intermediate" rather than as a drug.

#### Types of Crystal Forms:

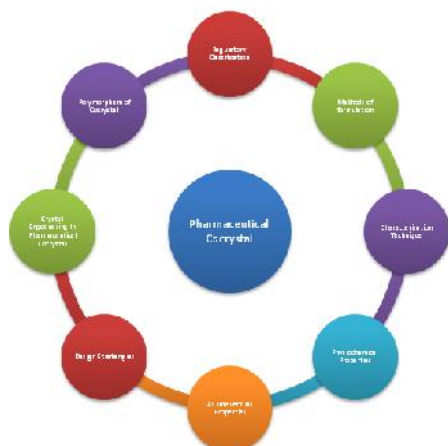
Pharmaceutical co-crystals are non-ionic supramolecular complexes and can be used to address physical property issues such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the API. This complex can be formed by several types of interaction, including pi-stacking, hydrogen bonding, and van der Waals forces. For nonionizable compounds co-crystals enhance pharmaceutical properties by modification of chemical stability, mechanical behavior, moisture uptake, solubility, dissolution rate and bioavailability.<sup>51,52</sup> The relationships between various solid forms are shown in (Fig.5).



**Figure 5:** Relationships between various solid forms

Further, co-crystals are considered advantageous in the following situations:

- Drug molecules lacking easily ionisable functional groups (such as those containing phenol, carboxamide, weakly basic N-heterocyclic) can be intermolecularly manipulated via co-crystals to tune their physicochemical properties,
- Compound having particular sensitive groups to treatment of acid and base,
- Overcoming problems in filterability through co-crystallizing a compound<sup>53</sup>.
- Co-crystallization covers major areas in pharmaceutical field which are shown in (Fig. 6).



**Figure .6:** Areas covered by co-crystals in various pharmaceutical fields

A solid can exist in two forms i.e. crystalline or amorphous. In crystalline form a solid can exist as polymorph, hydrate, solvate, or co-crystal. Mostly we prefer to deliver crystalline forms of active compounds mainly due to the inherent stability of crystalline materials and the impact of crystallization processes on purification and isolation of chemical substances. [54] Pharmaceutical co-crystal is a multiple component crystal in which at least one component is molecular and a solid at room temperature (the co-crystal former), and forms a supramolecular synthon with a molecule or ionic API<sup>55</sup>.

#### Hydrates and Solvates

Solvates are molecular complexes where one or more solvent molecules are incorporated within the crystal lattice in stoichiometric proportions. It is referred to as a hydrate when the solvent of crystallization is a water molecule<sup>57</sup>. Hydrates represent about 10% of the structures archived in the CSD<sup>58</sup> and it has been suggested that approximately 33% of organic compounds form hydrates, whereas solvates are less prevalent (10%).<sup>59</sup>

#### Polymorphs

Polymorphism refers to the ability of a compound to exist in more than one crystal form. The earliest reported polymorphic compound was benzamide discovered in 1832 by Wöhler and Liebig. The phenomenon of polymorphism is a scientific challenge in the pharmaceutical industry and its adverse effects is revealed in the prominent examples of rantidine hydrochloride and ritonavir.<sup>60,61</sup>

#### Salts

Salt formation has been the primary means to modify the physicochemical properties of an API. Indeed, approximately, 50% of marketed APIs are administered as Salts are formed when a compound that is ionized in solution forms a strong salts<sup>62</sup>. Salts are formed when a compound that is ionized in solution forms a strong ionic interaction with an oppositely charged counterion. Its success and stability is dependent on the relative strength of the acid or base and the acidity and basicity constant of the components involved.<sup>63</sup>

#### Pharmaceutical Cocryystal

Pharmaceutical cocryystals,<sup>64, 65</sup> multi-component crystals in which at least one component is a neutral API and the cocryystal former is a pharmaceutically acceptable ion or molecule, have recently been added to the landscape of crystal forms of APIs. Early literature on pharmaceutical cocryystals focused primarily on the crystal structures of pharmaceutical cocryystals. Perhaps, the earliest reported pharmaceutical cocryystal is the 1934 French patent which disclosed cocryystals of barbiturates.<sup>66</sup> Cairra and others reported the potential of complexes of sulphonamide drugs in drug development<sup>67</sup>

## 2. Supramolecular Chemistry

Supramolecular chemistry, described as "chemistry beyond the molecule" expands over several science disciplines such as classical inorganic and organic chemistry, material science and physics. The beginning of supramolecular chemistry can be traced back to the late 19<sup>th</sup> century through the introduction of transition-metal coordination chemistry Werner,<sup>68</sup> Emil Fischer's lock and key

mechanism in enzyme reactions and the discovery of cyclodextrins by Hebd. However, it was the pioneering works of Pederson<sup>69</sup>, Lehn and Cram in the discovery of crown ethers that ignited interest in supramolecular chemistry. Supramolecular chemistry extends beyond the realm of atomic and molecular chemistry to afford highly complex, well-defined supramolecular entities.<sup>70</sup> It emphasizes the use of intermolecular interactions in the self-assembly of molecules governed by their chemical and geometrical factors.

**Table 2:** Intermolecular Interaction

Intermolecular Interaction	Strength (kJ/mol)
Ion-Ion	100-350
Ion-Dipole	50-200
Hydrogen Bond	4-120
Dipole-Dipole	5-50
- Stacking	<50
Van der Waals	<5

### 3. Crystal Engineering

Crystal engineering, synonymous to solid state supramolecular synthesis, focuses on the synthesis and design of functional crystalline materials. It stems from the premise that the crystal, described as the perfect supermolecule<sup>71</sup> supermolecule par excellence,<sup>72</sup> is the de facto manifestation of self-assembly of molecules. Although the term was coined in 1955 by Pepinsky,<sup>73</sup> it is the pioneering work by Gerald Schmidt in 1971 that is generally considered to be the birth of crystal engineering<sup>74</sup>.

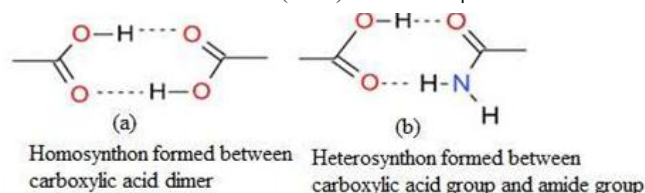
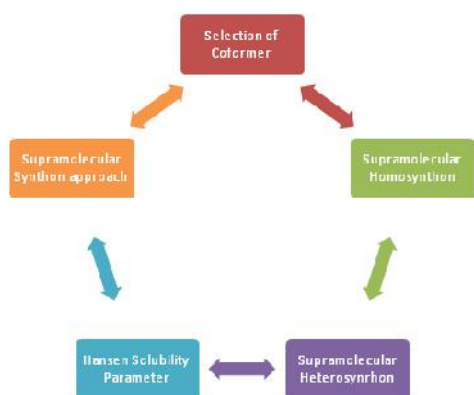
#### Selection of appropriate coformer and preparation of cocrystals [Supramolecular Synthron Approach]:

The term synthron was given by Corey in the context of organic chemistry and defined as “structural units within super molecules which can be formed and/or assembled by known or conceivable intermolecular interactions”. It’s a pattern that is composed of molecular and supramolecular elements. In crystal structure when crystal patterns repeat regularly, the pattern of interactions can be called a supramolecular synthron.

#### Supramolecular synthrons are further divided into

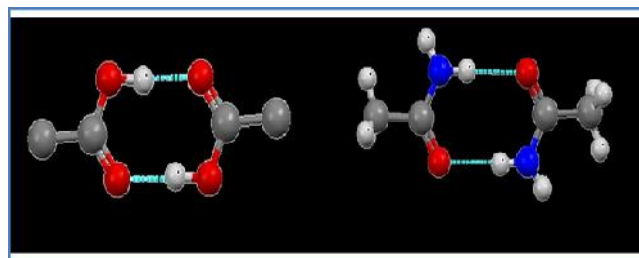
**Supramolecular Homosynthron:** Made up of identical self-complementary functionalities

**Supramolecular Heterosynthron:** Made up of different but complementary functionalist.

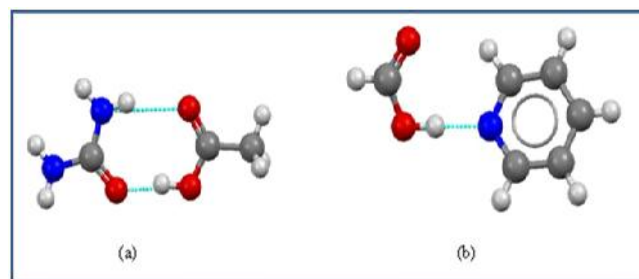
**Figure 7:** Selection of coformer

Desiraju coined the term “supramolecular synthron” and it is defined as, “structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions.”<sup>75</sup> The concept was extended by Zaworotko into two distinct classes: supramolecular homosynthrons and supramolecular heterosynthrons.<sup>76</sup>

Supramolecular homosynthron is the result of intermolecular interactions between identical self-complementary functional groups such as carboxylic acid dimers and amide dimers (Figure 8).

**Figure 8:** Illustration of (a) carboxylic acid supramolecular homosynthron and (b) amide supramolecular homosynthron

Whereas supramolecular heterosynthron are intermolecular interactions between two or more different but complementary functional groups such as carboxylic acid-amide and carboxylic acid-aromatic nitrogen (Figure 9).

**Figure 9:** Illustration of (a) Carboxylic acid-amide supramolecular heterosynthron and (b) Carboxylic acid-aromatic nitrogen supramolecular heterosynthron.

#### Cambridge Structural Database:

The Cambridge Structural Database (CSD) is an established primary repository for the experimentally determined 3D structures of organic and organometallic compounds. It is a structural visualization and analysis software developed by the Cambridge Crystallographic Data Centre (CCDC). The CCDC was founded by the University of Cambridge in 1965 with the primary objective: “advancement and promotion of the science of chemistry and crystallography for the public benefit.” The CSD comprises of over half a

million structures making it a comprehensive and highly curated scientific resource for crystal engineering. The CSD facilitates reliable and fast retrieval, visualization and analysis of experimentally measured crystallographic data to further understand the behavior of molecules and intermolecular forces within a crystal. This knowledge is fundamental to crystal engineering as it gives information concerning the type of intermolecular interaction, the geometrical preferences, the directional characteristics and the types of supramolecular synthons involved.

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#### 4. Advantages of cocrystal approach

Co-crystals having several advantages such as no necessitate to make or break covalent bonds, as compared to amorphous solids it is stable crystalline form, theoretical ability of all types of drug molecules such as weakly ionizable/non-ionizable to form cocrystals, the existence of numerous potential counter-molecules such as food preservatives, pharmaceutical excipients, additives, and other APIs, the only solid form that is designable via crystal engineering patentable expanding IP portfolios and can be produced using solid-state synthesis green technologies high yield, no solvent or by-products<sup>77</sup>.

##### Newer developments in cocrystal formulation:

For drug delivery, it is required that the drug molecule in the cocrystal exerts its pharmacological effect. The addition of co-former may enhance or decrease or may not have any effect on the therapeutic activity of the drug molecule. The present development in structure prediction and property elucidation of cocrystals have led to increasing number of formulations being coming to market and these rapid improvements will facilitate greatly in overcoming the solubility related problems. Here are a few examples of cocrystals from recent literature showing improved solubility.

#### 5. Conclusion

In present work a new method was developed and forced degradation studies were carried out for the estimation of Phentermine hydrochloride in bulk and pharmaceutical dosage form. Forced degradation HPLC method was developed with the mobile phase system of MeOH: Water (0.2% TEA in the ratio of 30:70 v/v  $p^H$  adjusted to 3.5 with orthophosphoric acid). The flow rate of 1ml/min was used on  $C_{18}$  column (250×4.6 mm, 5 $\mu$ m particle size). The retention time of Phentermine hydrochloride was observed at 9.907 min The developed and validated stability indication HPLC method is found be linear, accurate, precise, specific and robust. Hence the method can be used

routinely for estimation of Phentermine hydrochloride in formulations.

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