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Ferric Maltol Of WBCIL: Optimized Absorption, Minimal Toxicity, And Sustainable Production For Chronic Iron Deficiency: The Best Is Always Better Than Good

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I. Introduction:

Iron deficiency is the most common cause of anaemia globally. It is frequently reported in patients with underlying inflammatory conditions, such as inflammatory bowel disease (IBD) and chronic kidney disease (CKD). The treatment goals are to treat the underlying cause, limit further blood loss or malabsorption, avoid blood transfusions in haemodynamically stable patients, relieve symptoms, and improve quality of life [1]. Ferric maltol is a new oral iron replacement therapy designed to optimize iron absorption while reducing the gastrointestinal adverse events associated with unabsorbed free iron. Oral iron supplementation has been considered standard treatment because of its established safety profile, lower cost, and ease of administration [1]. Ferric maltol has been studied in clinical trials. It is approved for treating adults with iron deficiency with or without anaemia. It is well-tolerated over long-term treatment for up to 64 weeks; an important consideration in patients with chronic underlying conditions such as IBD and CKD. The advantage of maltol is that it prevents the formation of iron hydroxide polymers which makes the iron easier for the body to absorb while stabilized in the ferric form, which, in turn, minimizes the potential for mucosal toxicity compared with ferrous iron. The iron in ferric maltol is highly bioavailable, which could allow lower doses of elemental iron to be used.

Ferric maltol comprises a complex of one ferric iron and three maltol anions and has the following molecular formula: $(C_6H_5O_3)_3Fe$. Maltol is also known as 3-hydroxy-2-methyl-4-pyrone. It is a naturally occurring sugar derivative found in many food products, which is stable at physiologic pH [2]. The complex remains strongly chelated in the intestinal lumen until the point of absorption when the greater affinity of iron for the iron transport receptor on the surface of luminal enterocytes promotes dissociation from maltol. Thus, there is no free iron in the gut to generate hydroxyl radicals, minimizing the risk of gastrointestinal toxicity [3].

II. General Information:

The chemical name of ferric maltol is 3-hydroxy-2-methyl-4*H*-pyrane-4-one iron (III) complex (3:1) and has the following structure (**Fig 1**), the brief chemical and physical data are presented in **Table 1** [4].

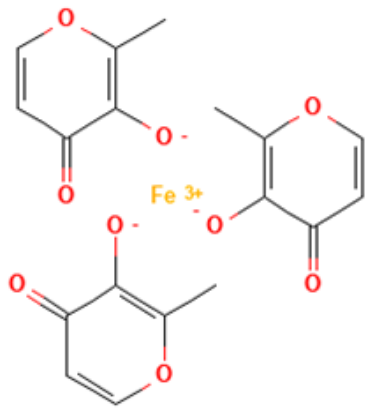


Fig 1. Structure of ferric maltol complex

Chemical and Physical Data[1]

Sl. No.		
1	Formula	$C_{18}H_{15}FeO_9$
2	Molar mass	431.154 g·mol^{-1}
3	CAS No.	[33725-54-1]

Table 1

General Properties

	Description	**:**	Deep brown, free-flowing powder.
	Solubility		0.5% w/v solution in water with opalescence.
	pH (of 5% w/v aqueous solution)	**:**	6.0 – 9.5
	Melting Point	**:**	~ 300.2°C
	Hygroscopicity	**:**	Slight Hygroscopic.
	Stereoisomerism	**:**	Ferric Maltol (Iron (3+) tris (2-methyl-4-oxo-4H-pyran-3-olate)) does not have any stereoisomerism.

III. Synthesis:

Synthesis of ferric maltol at WBCIL is carried out with the reaction of phenoxide of maltol in water in the presence of ferric chloride (**Fig 2)** to afford ferric maltol. The reaction temperature, mole ratio of the KSM and pH are the critical process parameters for the quality of the product.

The WBCIL process for the preparation of Ferric Maltol is carried out in the GMP facility and it is safeguarded by QbD. The critical process parameters such as sequential addition of raw material, control of temperature, modulation of pH, reaction time, isolation and spray drying are monitored critically. It is monitored analytically wherever applicable to afford the quality product. Modulation of pH during synthetic process is a critical process parameter for metal ligand binding. The process of manufacturing is eco-friendly as it is free from organic solvent.

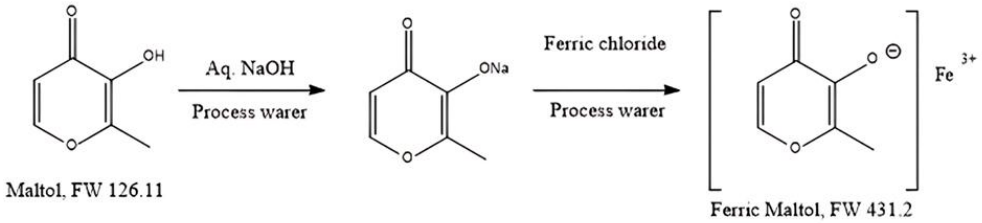
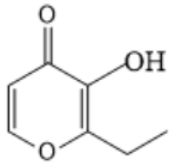
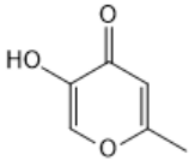


Fig 2. Preparation of Ferric Maltol

At WBCIL, the preparation process of ferric maltol is very stringent and it goes through three layers of analytical evaluation which are described below.

IV. Selection Of Maltol (KSM):

The starting material maltol is rigorously analyzed through different analytical methods viz., MS, NMR, IR and HPLC to control the related impurity from KSA which are as follows (**Table 2**):

Sl. No.	Impurity	Origin	Fate of the Impurity
1.	 Ethyl Maltol	KSM	This impurity is controlled in KSM Maltol and analysed by HPLC and MS. In maltol, ethyl maltol content is restricted by NMT 0.05%.
2.	 Allo Maltol	KSM	This impurity is controlled in KSM Maltol and analysed by HPLC and Proton NMR. In maltol, Allo maltol content is restricted by NMT 0.05%.

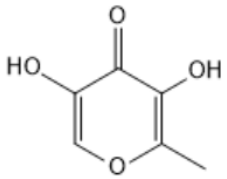
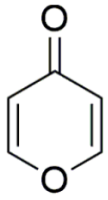
3.	 5-Hydroxy Maltol	KSM	This impurity is controlled in KSM Maltol and analysed by HPLC and MS. In maltol, 5-hydroxy maltol content is restricted by NMT 0.05%.
4.	 Pyrone	KSM	This impurity is controlled in KSM Maltol and analysed by HPLC and MS. In maltol, pyrone content is restricted by NMT 0.03%.

Table 2. Related impurities from KSM

Hence, we conclude that the starting material Maltol is free from above related impurities.

V. Isolation Of Product And Quality Attributes:

The final product is isolated through spray drying and at a particular range of temperatures. This temperature range is a critical process parameter. The higher the maximum temperature, the higher the degradation of ferric maltol (**Table 3**) which will lead to the poor product quality attribute [5].

Degradation Related Impurities:

Sl. No.	Impurity	Origin	Fate of the Impurity
1.	$Fe(OH)(Maltol)_2$	Degradation impurity at high temperature.	This impurity is controlled in the final API as NMT 0.05%. As in the HPLC of ferric maltol, no peak was observed below the RT of maltol.
2.	$Fe(OH)_2Maltol$	Degradation impurity at high temperature.	This impurity is controlled in the final API as NMT 0.05%. As in the HPLC of ferric maltol, no peak was observed below the RT of maltol.

Table 3. Degradation related impurities

Hence, we conclude that the WBCIL product is free from degradation-related impurities.

The above logic is supported by HPLC analysis (**Fig 3**) of the final product [6]. The ferric maltol undergoes hydrolysis in the mobile phase and shows the purity of only maltol. The purity of ferric maltol is about 100% without any peak of impurity. [***Condition of HPLC:*** Column-Agilent Zorbax SB C18 (250*4.6 mm* 5µ). Mobile phase: (A) 0.1% of orthophosphoric acid in water. (B) 100% methanol. Mobile phase composition A-90% and B-10%. Elution mode – Isocratic. Flow rate 1.0 ml/ min. Detector: UV. Wavelength 280nm. Diluent- Water: MeOH: :50:50]. This confirms the purity of the complex and the absence of any related impurity.

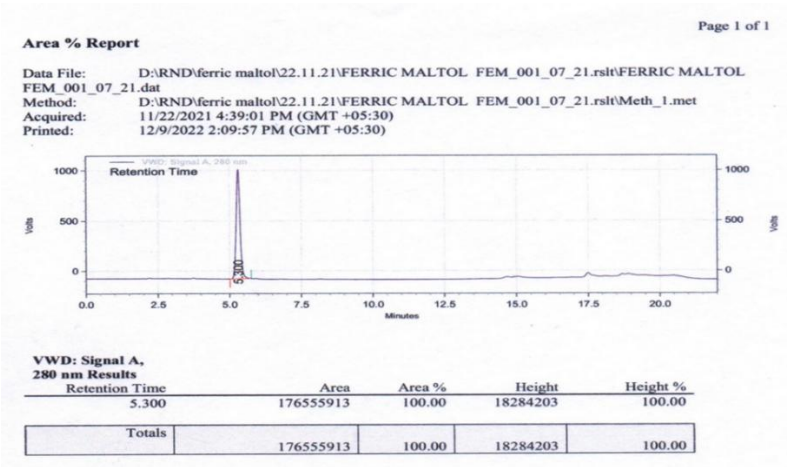


Fig 3. HPLC of Ferric Maltol

Another advantage of Ferric maltol of WBCIL as it is free from any nitrosamine impurity.

The probability of the presence of nitrosamine impurities [7,8] was nullified by critical risk assessment. It was also confirmed by a doped test. For the sake of argument if we consider that contamination may occur in the ferric maltol process due to environmental air, the corresponding nitrosamine impurity will be decomposed in acid-catalyzed media (aq. $FeCl_3$) as per the following mechanistic pathway [9] (**Fig 4**):

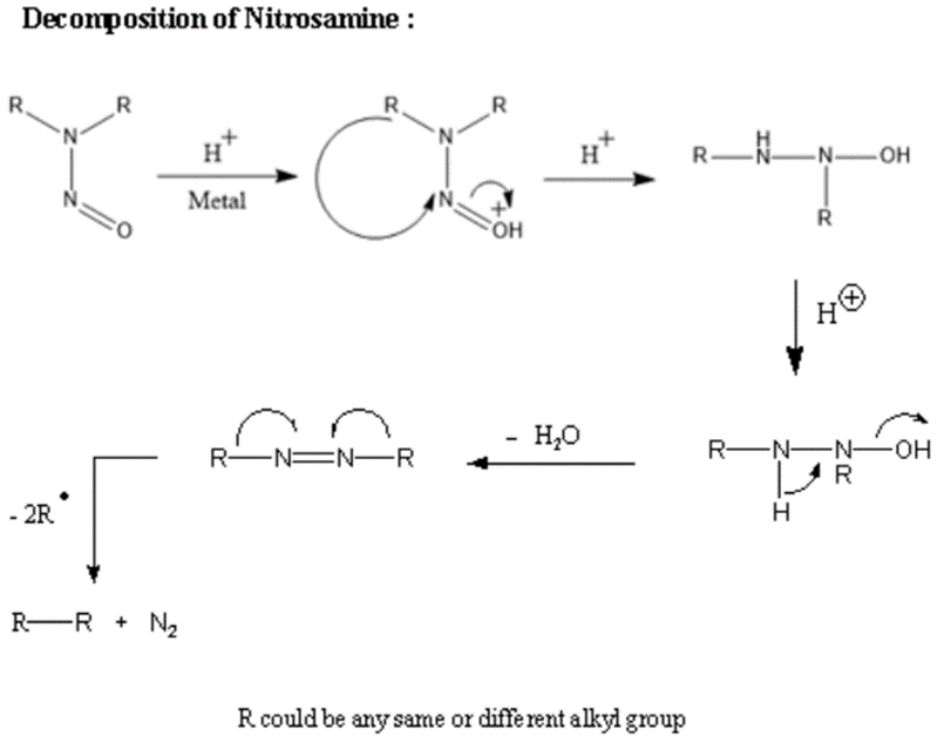


Fig 4. Degradation pathway of nitrosamine impurity

VI. UV-Visible Spectroscopy:

The structure of ferric maltol of WBCIL was further confirmed by UV-visible spectra (**Fig.8**). The analytical results show λ_{max} 224, 306 and 411 nm and it is in concurrence with literature [10,11]

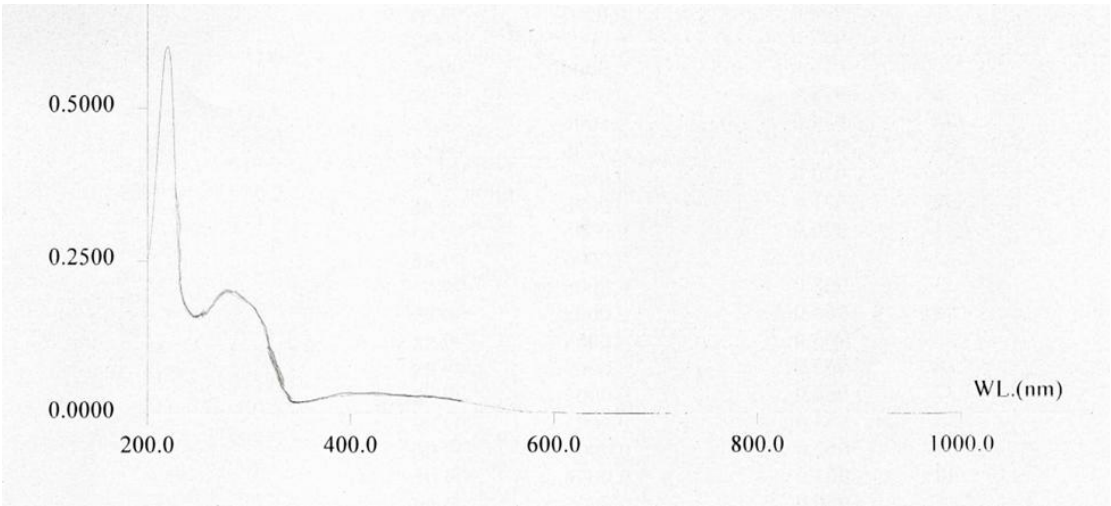


Fig. 5. UV-visible spectrum of ferric maltol of WBCIL

The wavelength is due to the transition from π -π* in a conjugated molecule depending on the energy gap between the HOMO and LUMO. This energy gap depends on the conjugated system of the molecule being studied. The UV-Vis spectra clearly reveal the involvement of Ligand-Metal-Charge-Transfer (LMCT) along with Metal-Ligand-Charge-Transfer (MLCT). Therefore, by measuring the UV spectrum of a molecule, structural information can be derived about the nature of the conjugated pi-electron system present in the complex.

VII. Infrared Spectrophotometry:

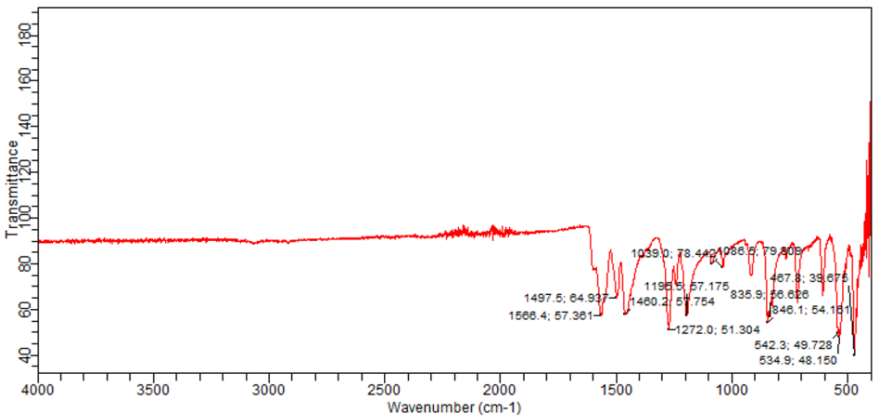


Fig 6. IR Spectra of Ferric Maltol of WBCIL

Assignment in cm $^{-1}$

C=O	C=C	Fe-O
About 1600	1566 and about 1497	467

Table 4

The above IR interpretation **(Fig 6)** confirms the structure of ferric maltol. The absence of peak at about 3262 cm^{-1} proves the absence of non-bonded or free maltol in the WBCIL complex of ferric maltol (**Table 4**). The intensity of C=O frequency is weak due to hydrogen bonding. It is interesting to note that the coordination of carbonyl oxygen of maltol to iron is evident from the decrease of stretching frequency by about 45 cm^{-1} compared to free maltol [10]. The peak at about 467 cm^{-1} reveals the metal-oxygen bonding.

VIII. Differential Scanning Calorimeter (DSC):

The DSC study of Ferric Maltol of WBCIL reflects the melting point about 300.2 degrees C, which is in concurrence with the literature value [12]. The DSC analysis of ferric maltol reveals a sharp endothermic peak corresponding to its melting point, indicating thermal stability up to this temperature and confirming the crystalline purity of Form A. In the TGA profile, the initial weight loss corresponds to the release of moisture or loosely bound water, showing minimal hygroscopicity. A secondary weight-loss stage reflects the onset of compound degradation, highlighting the stability range for formulation. This thermal stability profile supports ferric maltol's suitability for stable formulation in various storage conditions, minimizing degradation and ensuring product longevity.

IX. Mass Spectroscopy:

The ESI (positive mode) spectra show the base peak at m/z 127 (Maltol +1) and m/z 199 (Maltol + Iron + NH_3/H_2O). This confirms the structure of Ferric maltol manufactured by WBCIL [11].

X. Thermo Gravimetric Analysis (TGA):

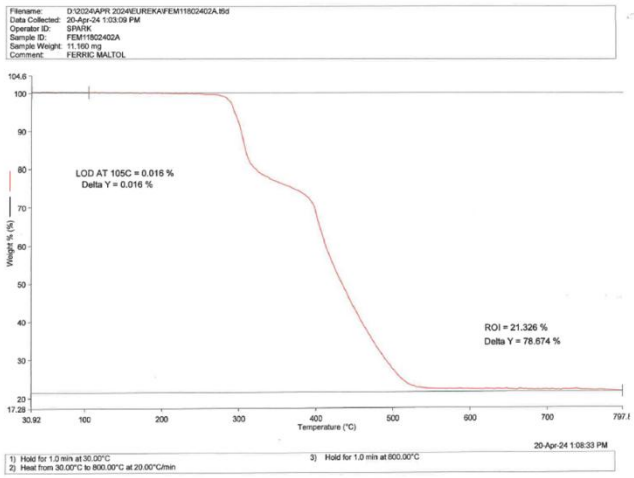


Fig 7. TGA of ferric maltol of WBCIL

The above diagram indicates the LOD at 105 deg C is about 0.016% (**Fig 7**) with Delta Y is about 0.016%.

- The first low weight loss step is due to the loss of bonded water in the complex.
- The second weight loss is due to the degradation/decomposition (about 400 degrees C) of the residual complex.
- Weight loss in the third step occurs due to combustion of compounds such as residual carbon from complex breakdown or burn off of complex [12].

XI. The Solid-State Morphology:

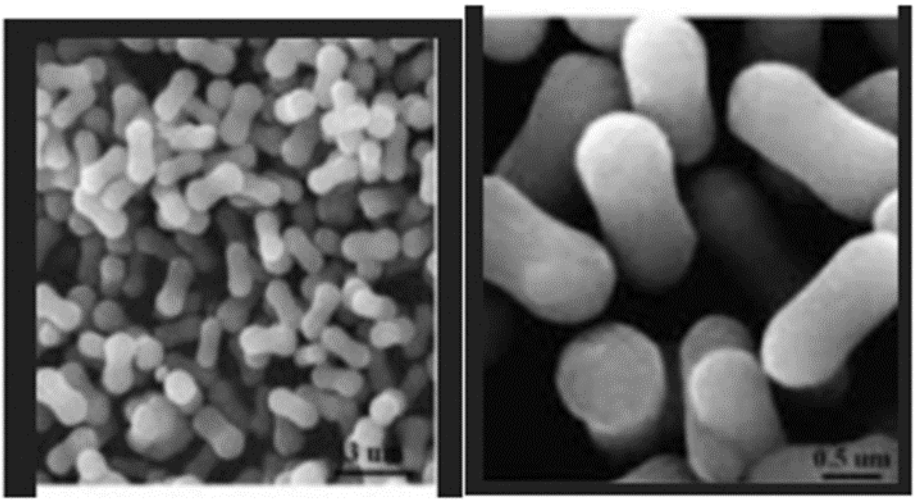


Fig. 8. *Solid-State Morphology* of ferric maltol of WBCIL

The above figure reveals the microscopic view of ferric maltol which has uniform and regular cylindrical structure (**Fig. 9**). In this image, the white portion indicates outer layer of ligand which has low electron density [13]. The advantages of the cylindrical-shaped ferric maltol are low displaceable iron content, high binding affinity with the ligand, slow-release rate and safe transportation to the receptor site**.**

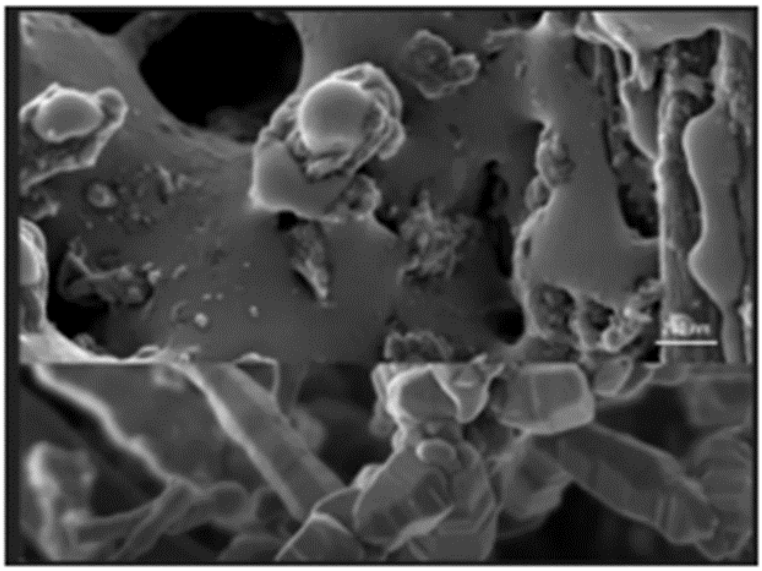


Fig. 9. High-resolution microscopic view of ferric maltol of WBCIL

The high-resolution microscopic view (**Fig. 10**) of the inner sphere cylindrical structure [13] reveals the totality of the morphology. The black hole portion indicates the iron core which is the inner part of the metal complex. This is black in nature due to high electron density of metal ion.

Lucidly the authors propose the following three-dimensional cylindrical structure of ferric maltol (**Fig. 11**) as follows:

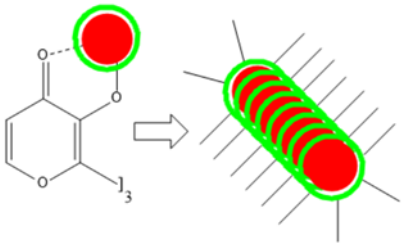


Fig. 10

The red spot indicates the metal ion, while the green circle represents the organic moiety of maltol; the black straight lines correspond to the methyl group.

XII. Polymorphism:

Polymorphism plays a crucial role in pharmaceuticals by influencing **solubility, stability, and bioavailability**, which directly affect drug performance. WBCIL has developed ferric maltol in **Polymorphic Form A** (**Fig.12**), which offers significant advantages over other forms (form ensuring better therapeutic outcomes, consistent manufacturing quality, and enhanced stability [14].

Structural Stability and Defect Control

Form A exhibits **high packing density**, which increases structural stability by minimizing **Schottky and Frenkel defects [15]**. These defects, often found in less ordered crystal forms, can reduce stability, causing degradation during storage or environmental changes. The compact and rigid crystalline structure of Form A minimizes the risk of such transitions, ensuring **consistent product quality** throughout its shelf life.

Solubility and Bioavailability Benefits

Polymorphic Form A has **superior solubility and faster dissolution** compared to other polymorphs, which facilitates **efficient absorption** in the gastrointestinal tract. This ensures that iron is bioavailable at lower doses, reducing the risk of common side effects such as **nausea, constipation, and abdominal discomfort** associated with ferrous iron supplements. Faster dissolution also contributes to more **predictable pharmacokinetics**, which is beneficial for long-term iron therapy, particularly in patients with **IBD and CKD** who may struggle with iron malabsorption [16,17].

Therapeutic Relevance of Form A

Form A's enhanced bioavailability allows **lower elemental iron doses** to achieve therapeutic levels, improving patient adherence by minimizing side effects. Its stability ensures the drug maintains its intended **clinical efficacy throughout storage and use**, reducing the risks associated with polymorphic transitions. These properties make Form A particularly well-suited for patients requiring **chronic iron therapy** with a well-tolerated, efficient formulation.

Manufacturing and X-ray Diffraction (XRD) Analysis and Verification

The EMA assessment report indicates that aqueous synthesis of ferric maltol yields either Form A or Form C [18]. Form C corresponds to Form II of EP3160951B1 due to their similar melting points (~293 °C). Consequently, the API with a melting point near 300 °C (e.g., WBCIL API and Form I of EP3160951B1) must be Form A [19]. Forms III and IV, being daughter polymorphs obtained from organic solvent mixtures of Forms I and II, are not directly relevant to aqueous synthesis processes.

The identity of Form A is confirmed by **X-ray diffraction (XRD) analysis.** So, far XRD is concerned, the characteristic peak of Form A is at 2-theta 15.6 and 22.5 deg. This matches with the WBCIL product of ferric maltol as these characteristic peaks appear at 2-theta 15.58 and 22.56 degrees. *Further, the PXRD of Form A should have two or more, three or more, four or more or five or more of the peaks at 2-theta 11.4, 12.8, 13.7, 16.9, 20.0, 20.7, 23.0, 23.8, 25.2, 25.8 or 28*[10]. The ferric maltol of WBCIL have the above peaks at 2-theta 11.49, 12.84, 13.79, 17.0, 20.0, 20.68, 20.56, 22.95, 23.78, 25.14, 25.72 and 28.0. This XRD data proves the exclusivity of Form A of ferric maltol manufactured by WBCIL.

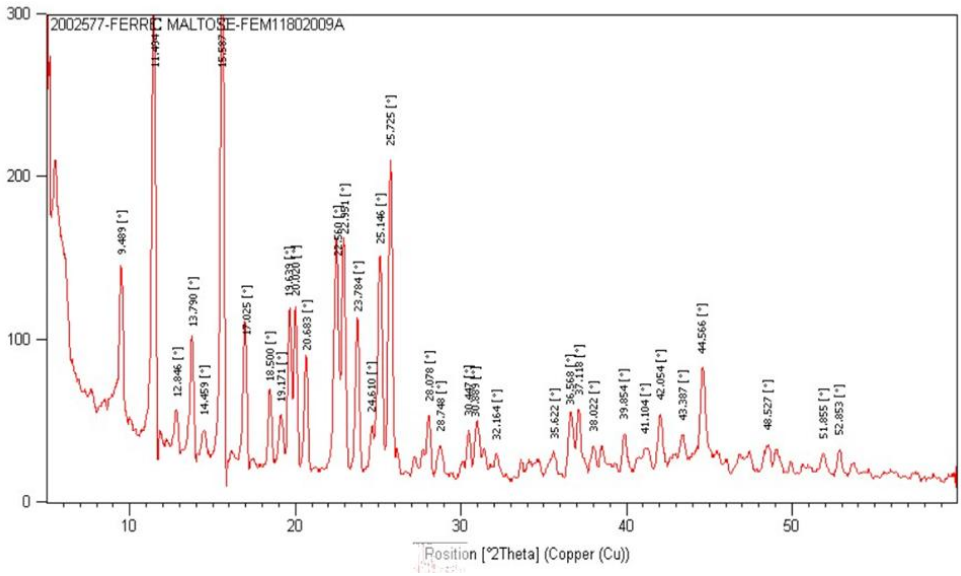


Fig 11. XRD of Form A of ferric maltol

The polymorphic form of Ferric maltol 'Form A' has higher solubility as compared to the other known polymorphs [18] along with its higher dissolution rate and consequently higher bioequivalence and bioavailability.

Comparison of Form A of WBCIL with Literature:

The below figure (**Fig. 13**) represents the concurrence of 2-theta value of ferric maltol prepared by WBCIL and that of literature value [18].

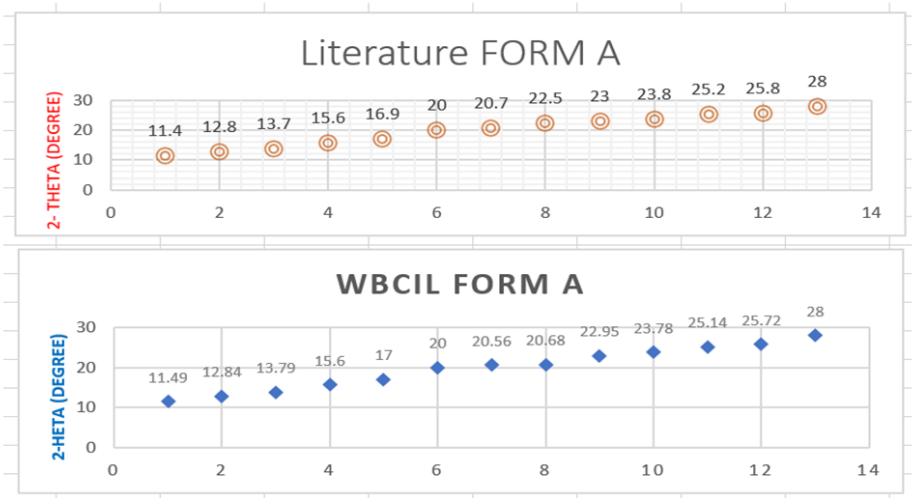


Fig. 12. XRD of Form A of WBCIL *vs*. Literature.

XIII. Hausner's Ratio:

The **Hausner ratio** is a number that is correlated to the flowability of a powder. Hausner's ratio was calculated by the formula = D_T / D_b; where, D_T = tapped density; D_b = bulk density *The **Hausner** ratio is used as an indication of the flowability of a powder. A Hausner ratio greater than 1.25 - 1.4 is considered to be an indication of poor flowability.*

The ferric maltol of WBCIL has having bulk density of 0.66 gm/CC and the corresponding tapped density is 0.82 gm/CC. Hence the ***Hausner*** ratio is 1.24; this indicates fair flowability of ferric maltol manufactured by WBCIL [20].

XIV. Toxicity Data Of Ferric Maltol:

The toxicity data of ferric maltol manufactured in WBCIL has gone through a rigorous Ames test and found it be safe [21].

XV. Potential Genotoxic Impurity In Ferric Maltol:

During the manufacturing process of Ferric maltol at WBCIL none of the following reagents are used in complete or by parts (**Fig 5**). None of the raw materials or intermediate have the structural similarity as per the below figure, Hence the ferric maltol manufactured at WBCIL is free from any potential genotoxic impurity [22].

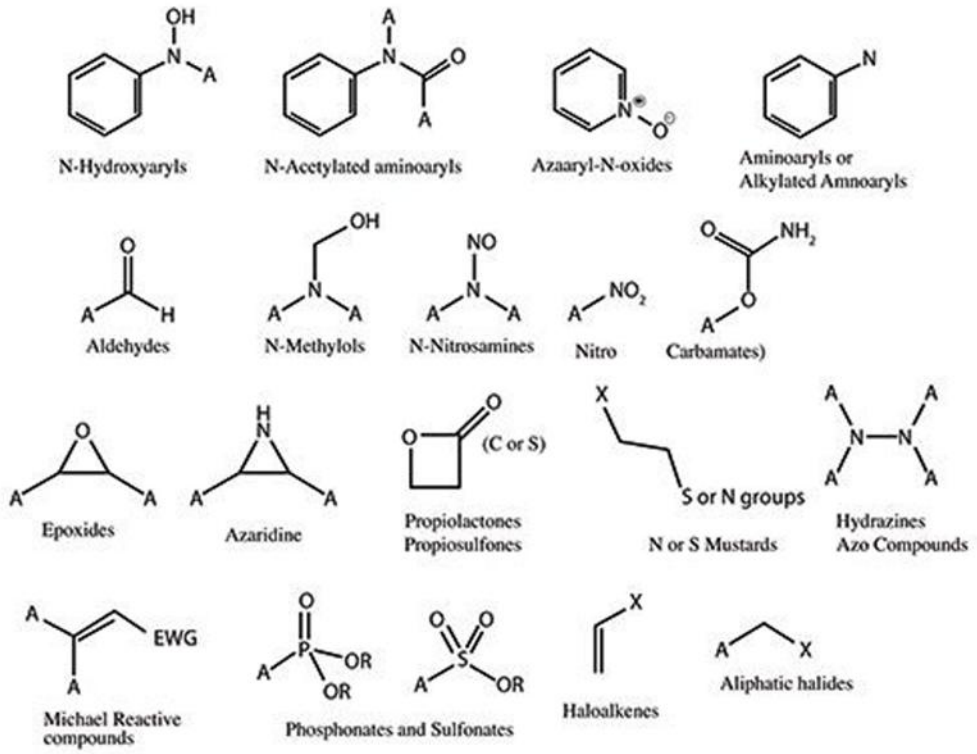


Fig 13

XVI. Other Quality Attributes:

The other quality attributes of ferric maltol manufactured by WBCIL is overwhelming. Comprehensive analytical testing was conducted and found that the elemental impurities are far below the threshold value compared to ICH guideline [23]. Heavy metals (such as lead), arsenic, copper and zinc present in the ferric maltol are far below the safe exposure limit along with the far lower content of chloride. The maltol, ferric content pH value is also well satisfactory.

Microbiological testing is crucial for ensuring the safety of any product, particularly for applications in the pharmaceutical industry. The ferric maltol sample of WBCIL demonstrated negligible yeast and mould content, indicating low levels of these potential microbial contaminants. Moreover, the absence of E. coli and Salmonella confirmed the supreme quality of ferric maltol, signifying the absence of these pathogenic bacteria. These microbiological findings contribute to the overall safety profile of the WBCIL-produced ferric maltol [24].

XVII. Stability Study:

The fascinating quality of ferric maltol manufactured by WBCIL was established by the stability study [25]. The stability study of ferric maltol was carried out in accelerated (40±2 deg C, 75±5% RH) and real (long term) time (30±2 deg C, 65±5% RH) conditions for three commercial batches. The quality parameter studies were carried out in terms of description, pH, LOD, iron content, maltol content and XRD. The end results were very encouraging and found that the commercial batches of ferric maltol of WBCIL was complying the specified quality attributes.

XVIII. Why The Ferric Maltol Of WBCIL Is The BEST:

The synthetic process is eco-friendly as it is free from organic solvents. The synthetic process is robust with QbD and the critical process parameters are well defined. Ferric maltol, particularly in the stable Polymorphic Form A, offers significant advantages as an iron supplement for patients requiring long-term therapy. Its enhanced stability and reduced defect density contribute to consistent manufacturing quality and improved shelf life. The Ferric maltol of WBCIL is free from related impurities, nitrosamine and genotoxic impurities. Hence, it is safer to use as it has better gastrointestinal tolerability compared to traditional oral iron supplements and Reduces side effects like nausea, constipation, and abdominal pain. The current aqueous synthesis is driven by regulatory demands for low levels of toxic heavy metals. The product is well characterized by several analytical methods viz., IR, NMR, MS, UV-Vis, pH, DSC and TGA. The manufacturing process of WBCIL affords Form A of ferric maltol exclusively. The Solid-State Morphology of ferric maltol is well-defined.

The high bioavailability and minimized gastrointestinal side effects of ferric maltol make it a well-tolerated option compared to traditional iron supplements, especially in patients with chronic inflammatory conditions like IBD and CKD. This stability, combined with the eco-friendly manufacturing process, underscores ferric maltol's suitability as a reliable, safe, and effective therapy for managing iron deficiency.

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