A REVIEW ON SOLUBILITY ENHANCEMENT OF CARBAMAZEPINE

Snehal Balkrushna Thombre, Anjali Vijendra Rathod , Sanskruti Sandeep Lembhe, Prerna Prakash Vaishnav, Sonal Satish Khandagale.
Gajanan Maharaj College Of Pharmacy,Chh. Sambhajinagar
snehalthombre82@gmail.com
Mrs. Tooba Khan (M.Pharm) Department Of Pharmaceutics.
Dr.Kavita Kulkarni (phd.M.Pharm)Department Of Quality Assurance.Gajanan Maharaj College Of Pharmacy,Chh.Sambhajinagar.

Abstract
The challenge of poor aqueous solubility in drug development significantly impacts bioavailability, therapeutic effects, and dosage levels, with up to 70-90% of drug candidates, particularly BCS Class-II drugs, facing solubility issues. These drugs are characterized by low solubility but high permeability. Various methods for enhancing solubility have been explored. Physical and chemical approaches include particle size reduction, solid dispersion, supercritical fluid technology, inclusion complex formation, pH modification, and the use of co-solvents. Nanotechnological approaches such as liposomes, nanoparticles, dendrimers, micelles, and metal-organic frameworks also improve solubility and bioavailability. Newer technologies, including microemulsions, self-emulsifying drug delivery systems, and supercritical fluid technology, have shown potential in enhancing solubility. Solid dispersions are particularly noted for increasing the bioavailability of poorly soluble drugs by improving wettability and porosity, though large-scale reproducibility remains a challenge, and no universal solution has been identified, necessitating further research. The review also highlights carbamazepine (CBZ) as a case study, summarizing various methods that have successfully improved its solubility and bioavailability in both in vitro and in vivo studies. The importance of solubility in achieving therapeutic effects across different administration routes is also emphasized.

Keywords:*Carbamazepine, Solubility, Dissolution, Crystallization, Solubilization techniques, BCS classification*

Introduction

Solubility:

Solubility is defined as the maximum quantity of solute that can dissolve in a given solvent or solution at a specified temperature. More than 90% of drug administered as orally drug absorption, bioavailability and pharmacokinetics profile are dependent on solubility parameter

The therapeutic effectiveness of a drug is closely tied to its bioavailability, which depends on the solubility of the drug. Solubility is crucial for achieving the desired drug concentration in systemic circulation to produce the intended pharmacological response. Only about 8% of new drug candidates exhibit both high solubility and permeability. According to the Biopharmaceutical Classification System (BCS), poorly soluble compounds are grouped into Class III (poor solubility, high permeability) and Class IV (poor solubility, poor permeability) drugs. Drug formulation, especially for parenteral (injectable) forms, presents challenges due to solubility

limitations, requiring methods to enhance solubilization. Solubilization methods for poorly soluble drugs depend on efficiency, stability, and biocompatibility. Common techniques include pH adjustment, cosolvent addition, micelle inclusion using surfactants, and complexation.

Factors affecting solubility

1. Partical Size
2. Temperature
3. Pressure
4. Nature of the solute & solvent
5. Molecular size
6. Polarity
7. Polymorphs
8. Rate of solution

a.Size of the particles
b.Temperature
c.Amount of solute already dissolved
d.Stirringo

Why solubility is increase?

- Improved efficacy
- Reduced variability
- Increased bioavailability
- Easy formulation
- Reduced side effect
- Improved stability
- Expanded drug development

Method To Improve Solubility Of a Drug

1.Physical Modifications

- **Particle Size Reduction**

Particle size reduction is a process that turns large, irregularly-shaped substances into smaller, more uniform particles. It's also known as milling, grinding, comminuting, or granulating.

Particle size reduction is important because it can: Improve product performance, Optimize product characteristics, Ensure compliance with regulations, and Create a safer product.

Particle size reduction is used in many industries, including pharmaceuticals, food production, and recycling: Pharmaceuticals
Particle size reduction helps create pharmaceutical products with the desired compression, dissolution, and flowability.

Recycling

Particle size reduction can help recyclers extract materials from microchips more efficiently.

Cleaning products

Particle size reduction helps ensure that cleaning product particles are too small to be inhaled by people or pets.

Some methods for particle size reduction include:

Microfluidizers

Use a high pressure pump to force a product stream through microchannels, exposing it to intense shear forces.

Jet milling

Uses high-pressure gas to create collisions between particles, breaking them into smaller pieces.

Laser ablation

Uses a laser beam to ablate particles, which are then carried away by a nitrogen gas jet stream.

The efficiency of particle size reduction depends on the type of equipment used. For example, a ball mill is less efficient than a drop weight crusher because of ineffective collisions.

- **Conventional Method**

- **Micronization**

Micronization is a technique that reduces the size of drug particles to improve their solubility and bioavailability:
Micronization increases the surface area of drug particles, which speeds up the dissolution rate. This technique can be used to improve the bioavailability of drugs that are poorly soluble in water.
Micronization is typically performed using mechanical methods like grinding, milling, or crushing. Common tools used for micronization include ball mills, jet mills, and high-pressure homogenizers.
Micronization can improve the amorphous property and structural disordering of drug crystals. It's a cost-effective technique for improving the dissolution of poorly soluble drugs.

- **Nanoparticle or Nano suspension**
Nanoparticles can improve the solubility of drugs that are poorly soluble in water or lipid media. This is because nanoparticles have a high specific surface area, which increases their dissolution rate and solubility.

- **Complexation**
Cyclodextrins (CDs), cyclic oligosaccharides obtained from enzymatic degradation of starch, are widely used to enhance the solubility, dissolution rate, and bioavailability of lipophilic drugs. The three major types of cyclodextrins—α, β, and γ—are composed of 6, 7, and 8 glucopyranose units, respectively. They have a torus structure with a hydrophilic exterior and a hydrophobic internal cavity, making them effective complexing agents for poorly water-soluble drugs like carbamazepine (CBZ).
Mechanism of Complexation: Cyclodextrin complexation enhances drug solubility by excluding high-energy water from the CD cavity, relieving ring strain, and utilizing hydrogen bonding, hydrophobic interactions, and Van der Waals forces.
Challenges with β-CD: β-CD is the most widely used, but its low aqueous solubility (1.85 g/100 mL at 25°C) and potential toxicity limit its use. Derivatives like hydroxypropyl β-CD and sulfobutylether β-CD have been developed to improve water solubility and reduce toxicity.
Studies on Solubility Enhancement of Carbamazepine:

1. **Spray-Drying Technique:-**
Carbamazepine (CBZ) was complexed with β-CD and hydroxypropyl methylcellulose (HPMC) and processed using spray drying.
The resulting microparticles were spherical (irregular with HPMC alone). Thermal and IR analyses indicated strong interactions between CBZ and the excipients. No polymorphic transition was detected. The spray-dried formulation showed superior dissolution rates in simulated gastric fluid compared to physical mixtures. However, the physical mixtures lacked homogeneity.
2. **Controlled Release Applications**:
CBZ-β-CD complexes were incorporated into HPMC matrix tablets.
The CBZ-β-CD complex exhibited significantly improved dissolution compared to non-complexed CBZ. Bioavailability in beagle dogs was six times higher than commercial controlled-release tablets (Tegretol 200 CR). The higher bioavailability

was attributed to the 7-fold increase in aqueous solubility provided by the complex.

3. **HPβCD Complexation:**
   In vivo studies showed the CBZ-HPβCD complex had 5.6 times greater absorption (AUC) compared to commercial tablets. The complex also showed faster absorption (Tmax of 0.5 hours vs. 1.4 hours for the tablet), indicating improved bioavailability.
   Factors affecting complexation :-
   1.Steric effects
   2.Electronic efforts
   a. Effect of proximity of charge to CD cavity
   b. Effect of charge density
   c. Effect of charge state of CD and drug
   3. Temperature, additives and co-solvent effects

- **Polymorph :-**
  Polymorphs can be used to enhance the solubility of drugs by creating crystals with different properties than the original compound:
  Different lattice structures
  Crystalline polymorphs have the same chemical composition but different internal crystal structures, which can lead to different physicochemical properties.
  Different lattice energies and entropies
  Different polymorphs have different lattice energies and entropies, which can improve the dissolution rate of drugs.
  Metastable polymorphs
  Metastable polymorphs are generally more kinetically soluble than thermodynamically more stable polymorphs.
- **Solid dispersion :-**
  This method involves forming inclusion complexes by mixing a drug with a carrier, such as cyclodextrin. The carrier's cavity must be large enough to accommodate the drug, but small enough to remove water. Some methods to form solid dispersions include:
  Kneding: In this method, a carrier is mixed with water to form a paste, then the drug is added and kneaded.
  Co-grinding: The drug and carrier are mixed with water, then passed through a sieve. The resulting granules are dried in a vacuum.
  Spray-drying: The drug is dissolved in a solvent, and the carrier is dissolved in water. The solutions are mixed, then dried using a spray dryer.
  Microwave irradiation: The drug and carrier are mixed and reacted in a microwave oven to form an inclusion.
  Supercritical fluid process:-
  SCFs are intermediates between pure liquids and gases. SCF techniques can be used to micronize drug particles.
  Hot metal extrusion:-
  Hot metal extrusion is one of the most commonly used technique to enhance the solubility and oral bioavailability of a poorly soluble drug as a beneficial technique for solid dispersion, which involves simple dispersion of a poorly water soluble API in an inert carrier (polymer), where the drug could exist in amorphous or crystalline
- Polymorph
- Pseudopolymorphs
- Complexation
- Physical Mixture
- Kneading Method
- Co-precipitation Method
- Inclusion Complexation
- Kneading Method
- Lyophilization
- Microwave irradiation Method

- Surfactant based Solubilization
- Microemulsion
- Solid Dispersion
- Physical Kneading
- Melting /Fusion
- Solvent Evaporation
- Spray Freeze Drying
- Hot melt Extrusion
- Chemical modification
- Pro drug approach
- pH Adjustment
- Buffer balance
- Derivatization,
- Salt formation.
- Polymeric micelles formation
- Self-emulsifying systems
- Miscellaneous
- Supercritical fluid process,
- Adsorption

Newer techniques for solubility & bioavailability enhancement

A) Liquisolid technique

-Liquisolid tablets

-Glassy solid solution

B) Spherical agglomeration

C) Sono crystallization

Till now which methods used to increase solubility of Carbamazepin ?

1.Solid dispersion

2.Porous starch

3.Crystal-habit modifying agents

4.Cryogenic spray processes

5.Pharmaceutical crystal engineering

Carbamazepine Drug profile:-

Chemical formula :- C15H12N2O

Molecular weight :- 236.2686

Carbamazepine belongs to anticonvulsant family it is used to treat epilepsy , trigeminal Neuralgia and acute manic and mixed episodes in bipolar 1 disorder.

Carbamazepine was discovered in 1953 by swiss chemist Walter schindler. It was first marketed in 1962. It is available as a generic medication. It is on the World health organization's list of essential Medicines. Carbamazepine is synthesized by reacting 5H-dibenz[b,f]azepine with phosgene, and then with ammonia .

The bioavailability of Carbamazepine is in the range of 75-80% of an ingested dose. after one 200mg oral extended-release dose of Carbamazepine in a pharmacokinetics study, the Cmax Carbamazepine were measured to be 1.9 ± 0.3 mcg/mL. The Tmax was 19 ± 7 hours. After several dose of 800 mg every 12 hour, the peak concentration of Carbamazepine were measured to be 11.0 ± 2.5 mcg/mL. The Tmax was reduced to 5.9 ± 1.8 hours. Extended-release Carbamazepine demonstrated linear pharmacokinetics over a range of 200-800mg.

Carbamazepine is 75% - 80% bound to plasma proteins. One pharmacokinetic study indicate that is 72% bound to plasma protein. Carbamazepine works for both seizures and trigeminal neuralgia by balancing signals between nerves. Carbamazepine is available as Carbatrol, Epitol, Tegretol, Tegretol XR, and generic carbamazepine in the following dosage forms that are taken by mouth.

- 100 mg, 200 mg, 300 mg, and 400 mg oral tablets
- 100 mg and 200 mg chewable tablets
- 100 mg/5 mL oral suspension
- 100 mg, 200 mg, and 300 mg oral extended-release capsules
- 100 mg, 200 mg, and 400 mg extended-release tablets

Carbamazepine should be stored at room temperature, between 68 F to 77 F (20 C to 25 C). It can be exposed to temperatures between 59 F to 86 F (15 C to 30 C) for shorter periods of time, such as when transporting it. Store in a cool, dry place in a tight container. Protect from light.

Most common side effects of Carbamazepin:-

- Dizziness
- Drowsiness
- Feeling unsteady when walking
- Nausea or vomiting

Serious side effect of Carbamazepine:-

1.Severe skin reaction

a. Painful red or purple skin that looks burned and peels off.
b. Flat red rash or blisters on your skin, mouth, nose, and genitals.
c. Red, painful, watery eyes

2.Blood disorder

a. Fever
b. Shortness of breath
c. Pale or yellowish skin
d. Easy bruising or bleeding
e. Frequent infection
f. Unusual weakness or tiredness
g. Dizziness, lightheadedness, or feeling like you are about to pass out
h. Headache
i. Fast or abnormal heartbeat

3.Heart Rhythm changes

a. Chest pain
b. Shortness of breath
c. Feeling dizzy,lightheaded, or fainting (feeling like you are about to pass out)
d. Changes in your heart rate or rhythm, such as a fast, slow ,pounding or skipping heartbeat

4.Liver damage

a. Nausea or vomiting
b. Stomach or belly pain
c. Fever
d. Weakness or unusual tiredness
e. Itching
f. Loss of appetite
g. Light-colored poop
h. Dark-colored pee
i. Your skin or the whites of your eyes turning yellowish in color (also called jaundice)

5.Low sodium level

a. Headache
b. Drowsiness
c. Muscle weakness or cramps
d. Nausea, vomiting, or loss of appetite
e. Tiredness or sleepiness
f. Dizziness
g. Weight gain
h. Restlessness or irritability
i. Change in your mental condition such as hallucinations, confusion, decreased awareness, or alertness
j. Seizures

6.Suicidal thoughts or action

a. New or increased thoughts of suicide or death
b. Suicide attempt
c. New or increased feelings of anxiety, depression, or other unusual changes in your mood or behaviour such as increased aggression or hostility.

Carbamazepine Uses:

- Effective in neurological and psychiatric disorders.
- Commonly prescribed as monotherapy for epilepsy.
- Drug of choice for partial seizures and most grand mal seizures.
- Effective for refractory partial epilepsy.
- Useful in alcohol withdrawal seizures.
- Preferred due to minimal weight gain and metabolic side effects.

- Suitable for patients with intellectual disability, balance issues, and cognitive dysfunction.
- Used in combination with ethosuximide for mixed-seizure patterns.
- Exhibits mood-stabilizing and anti-manic effects.
- Preliminary evidence suggests it may treat neonatal seizures.
- Widely used for treating Trigeminal Neuralgia.
- Therapeutic Drug Monitoring (TDM): Plasma levels of Carbamazepine are correlated with dosage, therapeutic effects, and side effect .

Literature Review

1. Jinal N. Patel , Dharmendra M. Rathod , Nirav A. Patel and moim K. Modasiya
2. Mittapalli Pavan Kumar , G. Y. Srawan Kumar, shanshak apte
3. Raj Kumar and Prem Felix siril
4. Raj kumar and Prem Felix siril
5. Abikesh p.k mahapatra, vinod patil, ravindra patil.

Materials and Methods

1. Polymers: Hydrophilic polymers improve solubility through various mechanisms.
2. Polyvinylpyrrolidone (PVP): Used to form solid dispersions.
3. Hydroxypropyl methylcellulose (HPMC): Enhances dissolution by increasing wettability.
4. Polyethylene glycol (PEG): Often used in co-solvent systems and solid dispersions.
5. Cyclodextrins: Form inclusion complexes with Carbamazepine to increase solubility.
6. Surfactants: Such as sodium lauryl sulfate (SLS) to reduce surface tension and increase wettability.
7. Lipid-Based Excipients: Lipid carriers like Gelucire or Capmul help in solubilizing lipophilic drugs.
8. Co-solvents: Ethanol, propylene glycol, and glycerin can be used to create solvent systems where Carbamazepine dissolves better.
9. Superdisintegrants: Croscarmellose sodium, sodium starch glycolate for immediate release formulations.

Methods :-

1. Solid Dispersion: Carbamazepine is dispersed in a water-soluble carrier matrix (such as PVP, PEG, or HPMC) to improve its dissolution rate. Solid dispersions can be prepared by techniques like solvent evaporation, fusion, and spray drying.
2. Inclusion Complexes with Cyclodextrins: Cyclodextrins form inclusion complexes with Carbamazepine by trapping its molecules in their hydrophobic cavity, thus enhancing its aqueous solubility.
3. Nanotechnology:
4. Nano suspensions: Reduce the particle size of Carbamazepine to the nanometer range to increase its surface area and enhance dissolution.
5. Nanocrystals: These are prepared by techniques like wet milling and high-pressure homogenization.
6. Cocrystallization: Carbamazepine can form cocrystals with other pharmaceutically acceptable molecules,
7. leading to enhanced solubility due to modified crystalline structure.
8. Hot-Melt Extrusion: Carbamazepine and polymers are heated and extruded to create a solid solution or dispersion, resulting in improved solubility and stability.

9. Micronization: Reducing particle size to the micrometre range increases surface area, enhancing the dissolution rate.
10. Supercritical Fluid Technology: Carbamazepine is processed with supercritical fluids (like CO2) to modify its crystalline structure or particle size.
11. pH Adjustment: Using buffers or salt formation to adjust the pH of the medium can increase Carbamazepine's solubility.
12. Lipid-Based Drug Delivery Systems: Formulating Carbamazepine with lipid-based carriers (e.g., self-emulsifying drug delivery systems, SEDDS) helps improve its solubility.
13. Amorphous Drug Forms: Converting Carbamazepine to its amorphous form, which lacks a defined crystalline structure, generally improves solubility over its crystalline form.
14. Each method has its advantages and specific applicability based on the formulation and desired drug release profile.

Conclusion:

Carbamazepine, an antiepileptic drug used to treat seizures and trigeminal neuralgia, has poor water solubility, which can result in slow and irregular absorption. Since drugs with higher solubility are generally absorbed more quickly, various techniques have been explored to enhance the solubility and dissolution rate of carbamazepine. One method is the use of solid dispersions, which, compared to physical and recrystallized mixtures, can significantly improve the drug's solubility and dissolution rate. Electrospraying is another technique that transforms the crystalline structure of carbamazepine into an amorphous form, producing nanobeads that improve solubility. Additionally, twin-screw melt granulation can yield drug loads of up to 90% (w/w) and enhance dissolution. Combining polyvinyl pyrrolidone (PVP K30) with sodium lauryl sulfate (SLS) has also been shown to successfully enhance solubility. Moreover, porous starch can be used as a carrier to improve both the solubility and dissolution rate of carbamazepine

Reference :

1.Savjani, K.T.; Gajjar, A.K.; Savjani, J.K. Drug solubility: Importance and enhancement techniques. Int. Sch. Res. Not. 2012, 2012, 195727. [CrossRef] [PubMed]

2.Gupta, J.; Devi, A. Solubility Enhancement Techniques for Poorly Soluble Pharmaceuticals: A Review. Indian J. Pharm. Biol. Res.2019, 7, 09–16. [CrossRef]

3.Patel, V.R.; Agrawal, Y.K. Nanosuspension: An approach to enhance solubility of drugs. J. Adv. Pharm. Technol. Res. 2011, 2, 81–87.[CrossRef] [PubMed]

4. Jagtap, S.; Magdum, C.; Jadge, D.; Jagtap, R. Research. Solubility enhancement technique: A review. J. Pharm. Sci. Res. 2018, 10,2205–2211.

5.Christian Leuner, Jennifer Dressman. Improving drug solubility for oral delivery Using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics, 2000, 50:47-

6.Kawabata Y, Wada K, Nakatani M, et al. Formulation design for Poorly water-soluble drugs based on biopharmaceutics classification System: basic approaches and practical applications. Int J Pharm 2011;420:1–10.

7. Spina E, Perugi G. Antiepileptic drugs: indications other than Epilepsy. Epileptic Disord 2004;6:57–75.

8.Lindenberg M, Kopp S, Dressman JB. Classification of orally Administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm 2004;58:265–278

9..Bhise S.B. and Rajkumar M., Effect of HPMC on Solubility and Dissolution of Carbamazepine Form III in Simulated Gastrointestinal Fluids, Asian J Pharm, 2008 ; Jan: 38-42.

10.Kobayashi Y., Ito S., Itai S., Yamamoto K., Physichochemical Properties and bioavailability of carbamazepine polymorphs And dihydrates, Int J Pharm, 2000 ; 193: 137-146.

11.Giunchedi, P.; Conte, U.; La Manna, A. A Swellable polymer as carbamazepine dissolution Rate enhancer. Boll. Chim. Farm. 1990, 129 (1), 17l 20.

12. Choudhury, S.; Nelson, K. F. Improvement of oral Bioavailability of carbamazepine by inclusion in 2-hydroxypropyl-b-cyclodextrin. Int. J. Pharm.1992, 85 (1–3), 175–180.

13. Zerrouk, N.; Chemtob, C.; Arnaud, P.; Toscani,S.; Dugue, J. In vitro and in vivo evaluation of Carbamazepine-PEG 6000 solid dispersions. Int.J. Pharm. 2001, 225 (1–2), 49 – 62.

14.Yogesh Thorat, Indrajeet D. Ghonjari, Avinash H. Hoamani, Solubility Enhancement Technique; A Review on conventional and novel approaches, International Journal of Pharmaceutical Science and Research,2011;Vol.2(10); 25

15.Kobayashi Y, Ito S, Itai S, Yamamoto K. Physicochemical properties and bioavailability of Carbamazepine polymorphs and dehydrate, International Journal of Pharmaceutics, 193, 2000, 137-146.