IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
July 2020 Vol.:18, Issue:4

A Review on – Different Complexation Method to Improve the Bioavailability of Curcumin

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Abhinay Sharma

Acharya & BM Reddy College of Pharmacy, India.

Submission: 26 June 2020
Accepted: 02 July 2020
Published: 30 July 2020

Keywords: Curcumin, Complexes, Bioavailability, Phospholipids

ABSTRACT

Curcumin is a natural compound with significant anticancer activity but due to its poor solubility and bioavailability, its application is limited. The curcumin concentrations of curcumin in patients, who had ingested 3.66 g curcumin orally, were 11.1 nmol/L and 1.3 μmol/L, respectively. In another study, patients receiving oral dosing of 4 to 8 g curcumin reached peak plasma concentrations of 0.41-1.75 μM, after 1-2h. To improve its bioavailability, the complexes of the Curcumin is the best method to improve the bioavailability of curcumin. The complexes are prepared with Phospholipids, soya lecithin, egg lecithin, chitosan and PEG 20000, etc. Some complexes are prepared by the refluxed method under the condition of temperature is not exceeding to 60°C for 4hrs with continuous stirring and some are prepared by using the solvent evaporation method. Complexation of bioactive compounds with phospholipids showed promising results in enhancing the bioavailability.

INTRODUCTION

Curcumin, [1, 7-bis (4-hydroxyl-3-methoxyphenyl)-1, 6-heptadiene-3, 5-Dione], is the major constituent extracted from the root of *Curcuma longa* Linn. Curcumin is a polyphenol that has powerful antioxidants. Curcumin was found to prevent colon, skin, stomach, duodenum, soft palate, tongue, sebaceous gland, and breast cancer. Curcumin could be considered a promising effective and safe preventive agent for cancer[1].

Although curcumin has been used widely as a therapeutic agent, however, the plasma and target tissue concentrations of curcumin are low, probably due, at least partially, low solubility, low permeability, and extensive conjugation metabolism (glucuronidation and sulfation) and reduction pathways[2].

Molecular weight of curcumin is 368.385g/mol and the Solubility in Water is 3.12mg/L at 25°C and 0.1mg/ml, in ethanol, 10mg/L in (DMSO) Dimethyl sulfoxide25mg/ml[3].

Literature review of the preclinical and clinical pilot studies suggest that the curcumin concentrations of curcumin in patients, who had ingested 3.66 g curcumin orally, were 11.1 nmol/L and 1.3 μmol/L, respectively. In another study, patients receiving oral dosing of 4 to 8 g curcumin reached peak plasma concentrations of 0.41-1.75 μM, after 1-2 h. Increasing the oral dosage of curcumin beyond that currently under examination is neither feasible nor desirable. Hence, it is highly to find the new formulation of curcumin to improve its bioasbsorption[3].

Recently the complexation of bioactive compounds with phospholipids showed promising results in enhancing the bioavailability because complexation of bioactive compounds.

Phospholipids increase the lipophilicity and therefore it is assumed to be highly permeable through biologic membrane[4].

Curcumin (bis-a, b-unsaturated b-diketone), commonly referred to as diferuloylmethane, is a low molecular, a natural polyphenolic compound found in the turmeric rhizome turmeric (curcumin longa). Due to its strong yellowish color, curcumin is primarily used as a food coloring agent. It has a wide variety of activities including anti-inflammatory, antioxidant, antiproliferative and antiangiogenic properties[5].

Curcumin low systemic bioavailability following oral dosing to limit the tissues that it can reach at an efficacious concentration to exert a beneficial effect, the attainment of such levels in the gastrointestinal tract, particularly the colon and rectum, has been demonstrated in both animal and human[6].

Unfortunately, the ingestion, biodistribution, metabolism, and elimination studies of curcumin have indicated only slow ingestion, fast metabolism, and curcumin removal as major explanations for low bioavailability. Numerous approaches have been employed to improve the bioavailability of curcumin. Nanoparticle, liposome, micelle, and phospholipid are the promising new formulation that seems to provide longer circulation, better permeability, and metabolic resistance[7].

Phospholipids play an important role in technology for drug delivery. It is an important carrier for those drug molecules that require controlled and sustained in vivo release due to faster body elimination. Lecithin/phosphatidylcholine (PC) and soya hydrogenated Phosphatidylcholine is an important component of phospholipids in the cell membranes. Soya lecithin and hydrogenated soya are voluntarily tuned to other nutrients and can improve their absorption when co-administered. Several experiments have shown that phospholipid complexation with phytoconstituents improves their bioavailability[8].

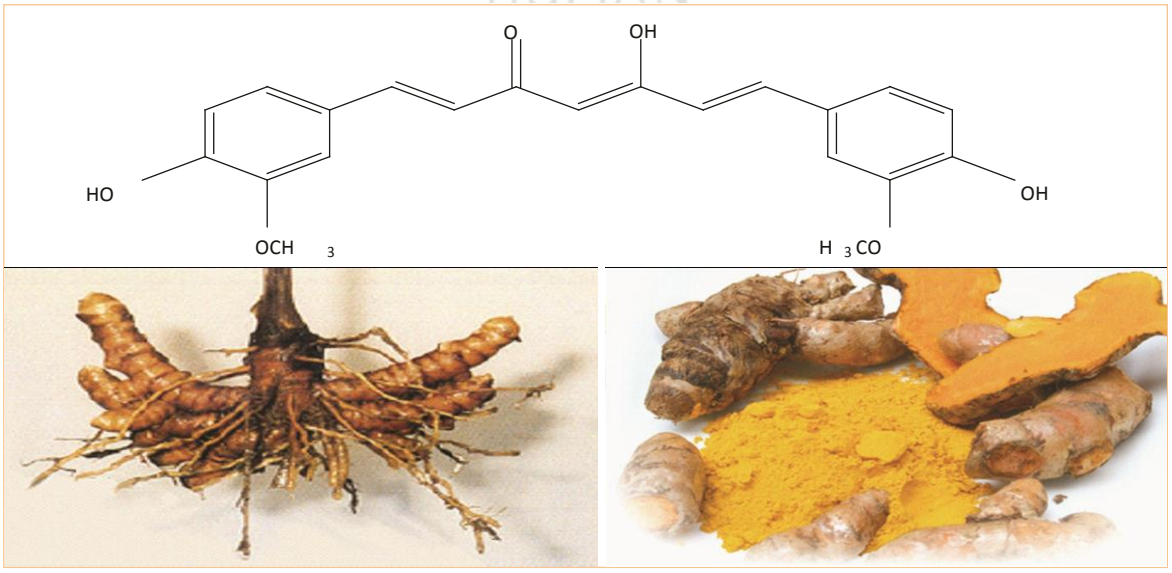

Figure No. 1: Photo of rhizomes of *Curcuma longa Linn* plant and chemical structure of polyphenolic curcumin compound[9].

For ages in indigenous medicine, turmeric powder has been widely used to treat various diseases including cough, diabetic ulcers, hepatic diseases, biliary disorders, rheumatism, sinusitis, and anorexia[10].

Turmeric boosts the total body muscle, expels air, enhances digestion, controls menstruation, dissolves gallstones, and alleviates arthritis according to Ayurveda practices[11].

Curcumin was studied in the modern era because of its health benefits, i.e. anti-aging, wound healing, and anticancer activities[12].

Curcumin was discovered two hundred years ago by Vogel and Pelletier and was obtained as a pure compound in 1842. Curcumin is light sensitive and nearly insoluble in water but can dissolve in methanol, dimethylsulfoxide, acetone, and ethanol[13]. Curcumin's chemical structure was reported in 1910, whilst Lampe and Milobedeska described the synthesis in 1913. The pharmacological actions of curcumin have since been studied extensively. In 1949, Schraufstatter and Bernt documented the antibacterial activity of curcumin, opening the door for other research that concentrated on the numerous actions of curcumin, such as anti-infective, anti-inflammatory, antioxidant, anti-coagulant, hypoglycaemic/anti-diabetic, anti-mutagenic, anti-carcinogenic, immunomodulatory, and wound healing effects[14].

COMPLEXATIONS METHODS

Preparation of M^{2+}-Curcumin Complex

Zinc sulfate ($ZnSO_4 \cdot 7H_2O$; 22%) was mechanically mixed with curcumin (M2 +: 1/1mol) in mortar until homogeneous powder mixture was obtained. Then a solution of glycerol/water (1 :1v / v) was applied to the mixture accompanied by mechanical shaning at 25 precautions before pasty combination was produced. Instead, after water evaporation, the pasty stock was dried at room temperature at 50 μC. Washing with purified water also removed free glycerol. Zn2 + curcumin pulverized complex was collected. Other complexes derived from another so urce of ion sulfate were prepared using the same process [9].

Preparation of curcumin–phospholipid complex

The complex was prepared with curcumin and HSPC at a molar ratio of 1:1. A weighed amount of curcumin and HSPC were taken in a 100ml round bottom flask and 20ml of dichloromethane was added. The mixture was refluxed at a temperature not exceeding 60◦C

for 2h. The resultant clear solution was evaporated and 10ml of *n*-hexane was added to it with continuous stirring. The curcumin–phospholipid complex was precipitated and the precipitate was filtered and dried under vacuum to remove traces of solvents. The resultant complexes (yield 88%, w/w) were kept in an amber-colored glass bottle, flushed with nitrogen, and stored at room temperature[15].

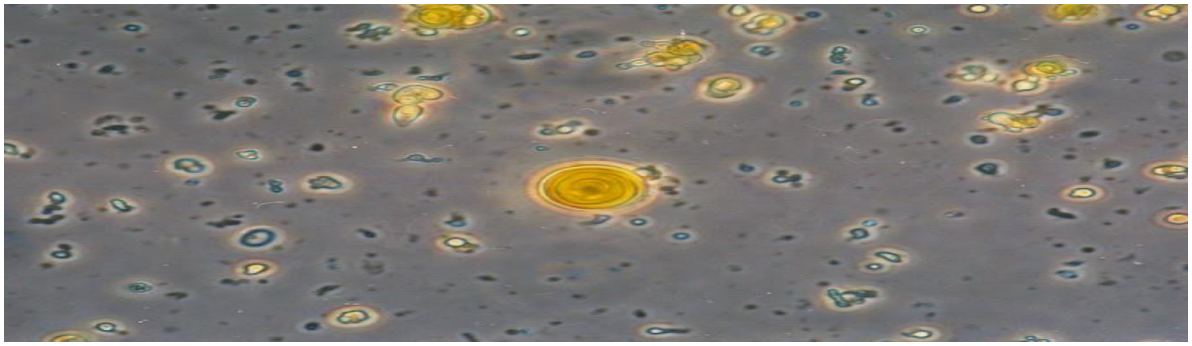

Figure No. 2: Microscopic views of curcumin–phospholipid complex with a magnification of 400X. Curcumin was intercalated in the phospholipid layer.

Preparation of CPC (Curcumin phospholipid complex)

The complex was prepared using the solvent evaporation method. In brief, curcumin, and phospholipid at a molar ratio of 1: 1 were weighed and then dissolved in 10 ml of absolute ethanol. Keep continuous stirring until the mixture was dissolved for about 2 h. Lastly, a transparent solution was formed after the resultant clear solution was evaporated for another 2 h. The semi-solid complex was dried under vacuum and stored at room temperature; the CPC was obtained[16]**.**

Preparation of CSP (Soluplus solidified powder)

Weighed the curcumin, phospholipid, and Soluplus at a mass ratio of 1:2:6. Next, the curcumi n and phospholipid in 10 ml anhydrous ethanol were dissolved and stirred until the mixture w as fully dissolved for around 2 h. Next Soluplus was added to the mixture being prepared and stirred until the mixture was completely dissolved. The solidified complex was then obtained by steamed fresh rotation solvents, scraping the solid drying under vacuum for 24h[16].

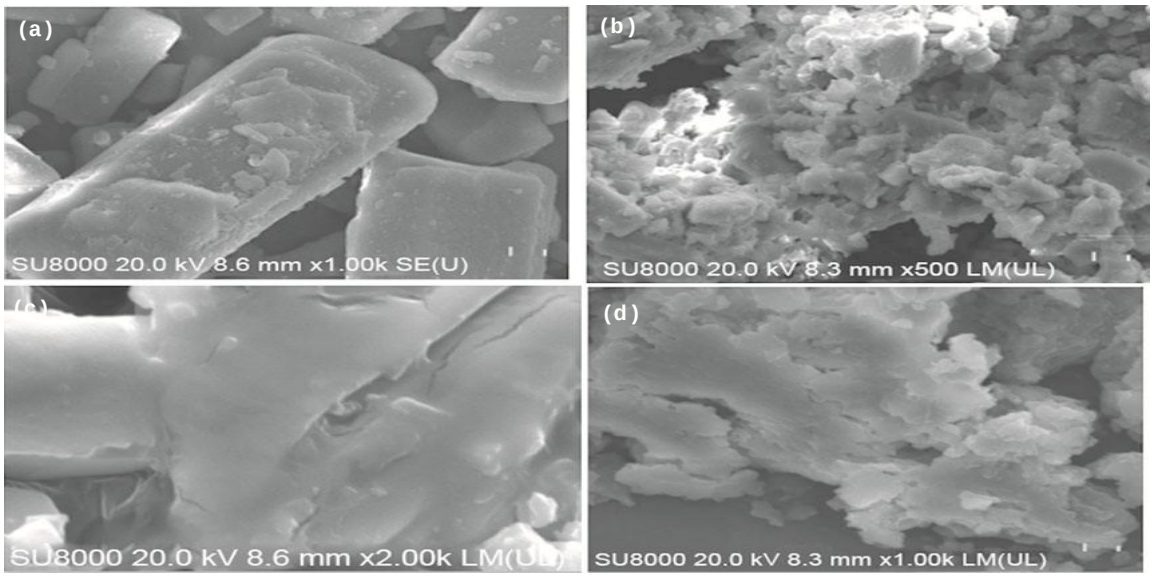

Figure No. 3: Scanning electron microscope photographs of pure curcumin (a), CPM (b), CPC (c) and CSP (d). CPM, curcumin physical mixture; CPC, curcumin phospholipid complex; CSP, curcumin phospholipid complex-Soluplus solidified powder.

Preparation of CU–PC-C Complex (phosphatidylcholine)

CU and PC were collected in a circular bottom flask at a molar ratio of 1:1 and dissolved in d ichloromethane at 20mL. This mixture was mixed on a magnetic stirrer at room temperature f or 2h. Under vacuum, the solvent was evaporated using rotary evaporator at 30C. The resultin g CU – PC C was washed with n-hexane, vacuum-dried and room temperature processed[17].

Preparation of CU–HSPC-C Complex (hydrogenated soya phosphatidylcholine)

CU and HSPC were taken at 1:1 molar ratio in a circular bottom jar and dissolved at 20mLin dichloromethane. At room temperature for 2h, this mixture was blended on a magnetic stirrer. The solvent was evaporated under vacuum at 30C using rotary evaporator. The subsequent C U-HSPC C washed with n-hexane, dried vacuum, and refined room temperature[17].

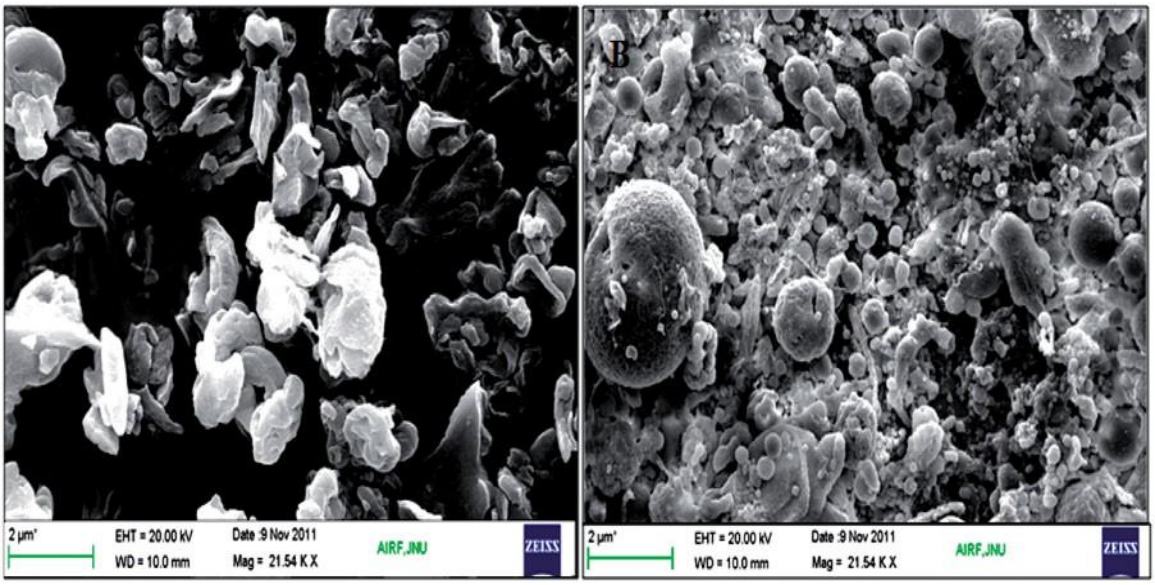

Figure No. 4: SEM of CU-PC-C (A) and CU-HSPC-C complex (B).

Preparation of curcumin and Soya Lecithin complexes

The complex was prepared with curcumin and soya lecithin at a molar ratio of 1:2. Weighed amount of curcumin and soya lecithin were taken into 500ml of round bottom flask and 50ml of dichloromethane was added. The mixture was refluxed at a temperature not exceeding to 60°c for 4hrs with continuous stirring. The curcumin-soya lecithin was precipitated and the precipitated was filtered with Buchner funnel and dried under vacuum oven for 24hrs to remove the traces of solvents. The resultant complexes was kept in an amber collared glass bottle, and stored at room temperature and Record the percentage yield[15, 17].

Ratios used in the formulation of Curcumin and lecithin soya complexes

15*368.385mg (mol con) of curcumin= 5.525g

30*645.9mg (mol con) of soya lecithin= 19.317g

Theoretical weight= 5.525g+19.317g= 24.842g

Practical weight of complexes= 12.56g

Figure No. 5: Prepared complexes of curcumin and soy lecithin

Preparation of curcumin and chitosan complexes

The complex was prepared with curcumin and chitosan at a molar ratio of 1:2. A weighed amount of curcumin and chitosan were taken into 500ml of the round bottom flask and 50ml of dichloromethane was added. The mixture was refluxed at a temperature not exceeding to 60°c for 4hrs with continuous stirring. The curcumin- chitosan was precipitated and the precipitated was filtered with Buchner funnel and dried under vacuum oven for 24hrs to remove the traces of solvents. The resultant complexes were kept in an amber collared glass bottle, and stored at room temperature and Record the percentage yield [15, 17].

Ratios used in the formulation of Curcumin and chitosan complexes

15*368.385mg (mol con) of curcumin= 5.525g

30*1526.5mg (mol con) of soya lecithin= 45.795g

Theoretical weight= 5.525g+45.795g = 51.32g

Practical weight of complexes= 51.01g

Figure No. 6: Prepared complexes of curcumin and chitosan

Preparation of curcumin and egg lecithin complexes

The complex was prepared with curcumin and egg lecithin at a molar ratio of 1:2. A weighed amount of curcumin and egg lecithin was taken into 500ml of the round bottom flask and 50ml of dichloromethane was added. The mixture was refluxed at a temperature not exceeding to 60°c for 4hrs with continuous stirring. After 4hrs transfer, the solution into petri dish dried and kept under vacuum oven for 24hrs to remove the traces of solvents. The resultant complexes were kept in an amber collared glass bottle, and stored at room temperature and Record the percentage yield [15, 17].

Ratios used in the formulation of Curcumin and egg lecithin

15*368.385mg (mol con) of curcumin= 5.525g

30*815.2mg (mol con) of soya lecithin= 24.45g

Theoretical weight= 5.525g+24.45g = 29.975g

Practical weight of complexes= 29.79g

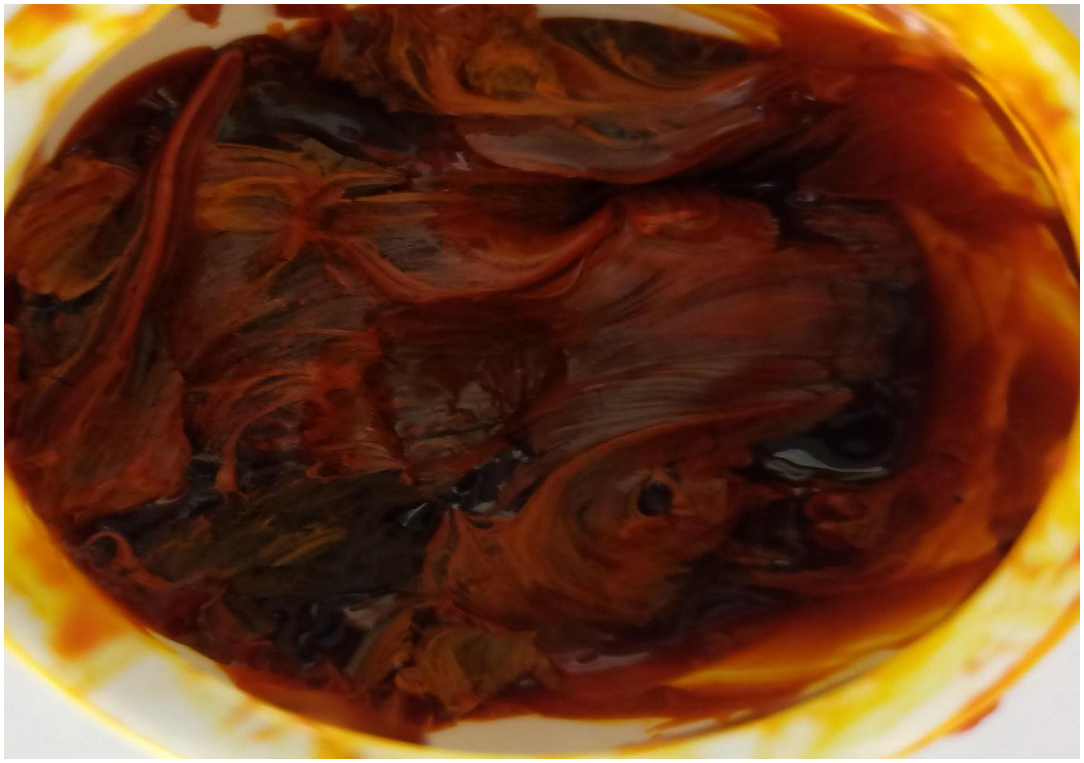

Figure No. 7: Prepared complexes of curcumin and egg lecithin

Preparation of curcumin and PEG 20000 complexes

The complex was prepared with curcumin and PEG 20000 at a molar ratio of 1:8. A weighed amount of curcumin and PEG 20000 were taken into 500ml of the round bottom flask and 50ml of dichloromethane was added. The mixture was refluxed at a temperature not exceeding to 60°c for 4hrs with continuous stirring. The curcumin-PEG 20000 was precipitated and the precipitated was filtered with Buchner funnel and dried under vacuum oven for 24hrs to remove the traces of solvents. The resultant complexes were kept in an amber collared glass bottle, and stored at room temperature and Record the percentage yield [15, 17].

Ratios used in the formulation of Curcumin and PEG 20000

5g of PEG 20000= 0.25g/mole

0.7367g of curcumin= 2g/mole

Theoretical weight= 5g+0.7367g = 5.7367g

Practical weight of complexes= 5.60g

Figure No. 8: Prepared complexes of curcumin and PEG 20000

CONCLUSION

The bioavailability of curcumin is a critical challenge for the treatment point of view. In this review, we presented the complexation method of curcumin with Phospholipids, soya lecithin, egg lecithin, chitosan and PEG 20000, etc. The complexes were prepared with curcumin and phospholipids at a molar ratio of 1:2 and in the preparation of curcumin and PEG 20000 the molar ratio is 1.8. A weighed amount of curcumin and phospholipids were taken into 500ml of the round bottom flask and 50ml of dichloromethane was added. The mixture was refluxed at a temperature not exceeding to 60°c for 4hrs with continuous stirring. The curcumin- phospholipids were precipitated and the precipitated was filtered and dried under vacuum oven for 24hrs to remove the traces of solvents. The resultant complexes were kept in an amber collared glass bottle and stored at room temperature. According to point of view, all the complexes are given good bioavailability of curcumin.

REFERENCES

1. Ferrari E, Pignedoli F, Imbriano C, Marverti G, Basile V, Venturi E, et *al*. newly synthesized curcumin derivatives: crosstalk between Chemico-physical properties and biological activity. J Med Chem. 2011;54(23):8066-77.
2. Vyas A, Dandawate P, Padhye S, Ahmad A, Sarkar F. Perspectives on new synthetic curcumin analogs and their potential anticancer properties. Current Pharm Dsg. 2013.1;19(11):2047-69.
3. O'Neil MJ, editor. The Merck index: an encyclopedia of chem, drugs, and bio. RSC Pub; 2013.
4. Lide DR, editor. Handbook of data on organic compounds. 5. Compounds 21600-27580, 1994.Pho-Zir. CRC Press.
5. Tapal A, Tiku PK. Complexation of curcumin with soy protein isolate and its implications on solubility and stability of curcumin. Food Chem. 2012 Feb 15;130(4):960-5.
6. Sharma RA, Gescher AJ, Steward WP. Curcumin: the story so far. Eur J Cancer. 2005 Sep 1;41(13):1955-68.

7. Anand KJ. Pain assessment in preterm neonates. Pediatrics. 2007 Mar 1;119(3):605-7.
8. Anand KJ. Pain assessment in preterm neonates. Pediatrics. 2007 Mar 1;119(3):605-
9. Khatik R, Dwivedi P, Shukla A, Srivastava P, Rath SK, Paliwal SK, Dwivedi AK. Development, characterization and toxicological evaluations of phospholipids complexes of curcumin for effective drug delivery in cancer chemotherapy. Drug delivery. 2016 Mar 23;23(3):1057-68.
10. Zebib B, Mouloungui Z, Noirot V. Stabilization of curcumin by complexation with divalent cations in glycerol/water system. Bioinorganic chem and applications. 2010;2010.
11. Li H, Sureda A, Devkota HP, Pittalà V, Barreca D, Silva AS, Tewari D, Xu S, Nabavi SM. Curcumin, the golden spice in treating cardiovascular diseases. Biotech Adv. 2020 1;38.
12. Garg PK, Prasad D, Aggarwal S, Mohanty D, Jain BK. Acute intestinal obstruction: an unusual complication of mucocele of appendix. Eur Rev Med Pharmacol Sci. 2011 Jan 1;15(1):99-102.
13. Codevilla CF, Barin JS, da Silva CD, da Silva TM, de Menezes CR. Incorporation of curcumin into nanostructured systems: A review. Ciência e Natura. 2015 Dec 15;37:152-63.
14. Mangal A, Kumar V, Panesar S, Talwar R, Raut D, Singh S. Updated BG Prasad socioeconomic classification, 2014: A commentary. Ind J public health. 2015 1;59(1):42.
15. Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: a short review. Life sci. 2006 27;78(18):2081-7.
16. Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Curcumin–phospholipid complex: preparation, therapeutic evaluation and pharmacokinetic study in rats. International journal of pharmaceutics. 2007 Feb 7;330(1-2):155-63.
17. Wang J, Wang L, Zhang L, He D, Ju J, Li W. Studies on the curcumin phospholipid complex solidified with Soluplus®. Journal of Pharmacy and Pharmacology. 2018 Feb;70(2):242-9.
18. Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Curcumin–phospholipid complex: preparation, therapeutic evaluation and pharmacokinetic study in rats. International journal of pharmaceutics. 2007 Feb 7;330(1-2):155-63.