THINK INDIA JOURNAL

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Formulation and Characterization of Curcumin Loaded Vesicular Formulation For Ocular Diseases

Deep Shikha Sharma, Vrinder Pal Singh*, Rajesh Kumar

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab (India)–144411

**Address for correspondence: Vrinder Pal Singh, Assistant Professor (Pharmacognosy), School of Pharmaceutical Sciences, Lovely Professional University, Phagwara - 144411, Punjab, India. Phone: +91-9814109800. E mail id: pannu.vicky@gmail.com*

Abstract

Curcumin (Turmeric) is an ancient plant used medicinally from many decades. **"Indian Saffron"** is another name of Turmeric. About 100 components have been isolated and main constituent is volatile oil having turmerone and other coloring agents which is curcuminoids. Liposome means "Lipid body" and their size ranges from 25-5000 nm. As the water solubility of curcumin is very low, so it stays in the body for short period of time and because of this we have to administer more amount of drug which leads to the toxicity in the body. To overcome this problem, curcumin vesicular formulation (liposome) was prepared, by using thin film hydration method, which is having high solubility in oily phase and the amount of drug added was less as compared to traditional dosage form. The prepared formulation can be used for Dry eye, Cataract, AMD, Glaucoma, Diabetic retinopathy, Iris iritis.

Key words: Turmeric, Curcumin, Liposomes, ocular diseases

INTRODUCTION

Eye anatomy and physiology: The organ of sense of sight is eye found in orbital cavity abounding with optic nerves. Eye has spherical shape, diameter is about 2.5 cm (1 inch) and it is protected with the help of fats along with bony walls of orbit [1]. It is often compared with camera and out of five senses it is utilized more. About 75% of information we receive around us is visual information [2].

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

External fibrous layer	**Sclera, cornea**
Middle vascular layer	**Ciliary body, choroid, iris**
Internal nervous tissue layer	**Retina**

One-sixth of the anterior part of eye is exposed, extrinsic muscles of eye includes the following [3]:

- **Superior rectus**
- **Inferior rectus**
- **Lateral rectus**
- **Medial rectus**
- **Superior oblique**
- **Inferior oblique**

CURCUMIN-A POTENTIAL DRUG

Curcumin (Turmeric) is an ancient plant used medicinally from many decades. **"Indian Saffron"** is another name of Turmeric. Also known as "Haldi" in North India and "Manjal" in south India. About 100 components have been isolated and main constituent is volatile oil having turmerone and other coloring agents which is curcuminoids. Demethoxycurcumin, 5'-methoxycurcumin, and dihydrocurcumin are main components of curcuminoids which are having good anti-oxidant properties. Volatile oils contains d-α-phellandrene, d-sabinene, cinol, borneol, zingiberene, as well as sesquiterpene [4]. Dose-limiting toxicity is not seen for curcumin when taken at doses of up to 8 g/day for a period of three months. Curcumin shows useful effects on a number of ocular diseases, such as:- Chronic anterior uveitis, Glaucoma, Diabetic retinopathy, Dry eye syndrome, Age related macular degeneration [5].

OPHTHALMIC PREPARATIONS

Ophthalmic preparations are mostly sterile formulations which can be in semi-solid form, liquid form meant for administration into eye cavity present in between eye lids and eye balls [6]. Some examples of conventional drug delivery system are shown in Table 1:-

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Table 1: Ophthalmic preparations (7)

EYE /OPHTHALMIC DROPS	Ophthalmic drops are mostly sterile, aqueous or oily preparations or suspensions or emulsions of single drug or combination of drugs. These are isotonic with respect to eye and pH value must be between 4-8 which is tolerable by eye otherwise there may be discomfort , irritation and decrease in bioavailability due to increased tearing.
EYE SOLUTIONS	These are also known as eye lotions. Ophthalmic solutions are sterile , aqueous preparation utilized for cleaning and rinsing of eyeballs. The composition includes excipients, preservatives etc.
EYE OINTMENTS	These are semi-solid preparations consisting of solid or semi-solid hydrocarbons base. After applying it converts into droplet form, having more bioavailability but main disadvantage is that it causes blurring of vision.
EYE SUSPENSIONS	Usually Eye suspension contains solid drug dispersed in vehicle and are homogenous in nature. But main disadvantage is that particle size should be kept in consideration while preparing suspension as large size of particle can cause irritation to eye.
CONTACT LENS SOLUTIONS	These are also sterile preparations and are isotonic in nature intended for used as wetting solution and sometimes as storage solutions.

LIPOSOMES

Liposome means “Lipid body” and their size ranges from 25-5000 nm. Normally cell wall consist of Lecithin which is natural substance made up by mixture of phospholipids, mainly containing phosphatidylcholine (PC) [8]. These are used for transporting substances directly into the body efficiently by facilitating absorption through mouth or by preventing breakdown by stomach acid [9]. Hydrophilic drugs can be entrapped and entangled in aqueous (liquid) compartment while hydrophobic drugs can be incorporated in lipid phase. The small-sized liposomes has increased rate of absorption as well as circulation time [10].

Liposomes comes from the family that is based upon Lipid delivery system. In 1961 liposomes were firstly prepared by Alec D. Bangham, a British hematologist and information regarding liposomes is discussed in Figure 1 [11].

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Due to their unique characteristics like morphology (which can be modified), particle size, zeta potential, efficiency of encapsulation, drug release profile etc. can improve the properties of drugs having low bioavailability [12]. The inner phase of the encircled vesicles can be separated from the outside phase, so that stability of the encapsulated drug can be improved. Doxorubicin, amphotericin B, nystatin, and vincristine are few examples of liposomal pharmaceutical formulations. The Various properties of drugs like bioavailability, absortion etc. can be increased due to liposomes having special characteristics like modifiable particle size, drug release profile, encapsulation efficiency, morphology and zeta potential etc [13].

Numerous parameters affecting bilayer formation are the following:-

1. The huge free energy difference between the Hydrophilic and hydrophobic phases promotes the bilayer structure to achieve lowest free energy level.
2. The driving force for bilayer formation of liposomes is the coupled interaction between hydrophobic and amphiphilic phospholipid molecules.
3. Supramolecular self- aggregation mediated through particular molecular geometry [14].

Mainly encapsulation to some extent is dependent on the partition coefficient or Log P of drug [15]. There are various systems present in human body which is responsible for clearance of liposomes are Reticulo-endothelial system (RES)/ Mononulcear Phagocyte system (MPS), Monocytes and Macrophages system present in liver, spleen and Lymph nodes [16].

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

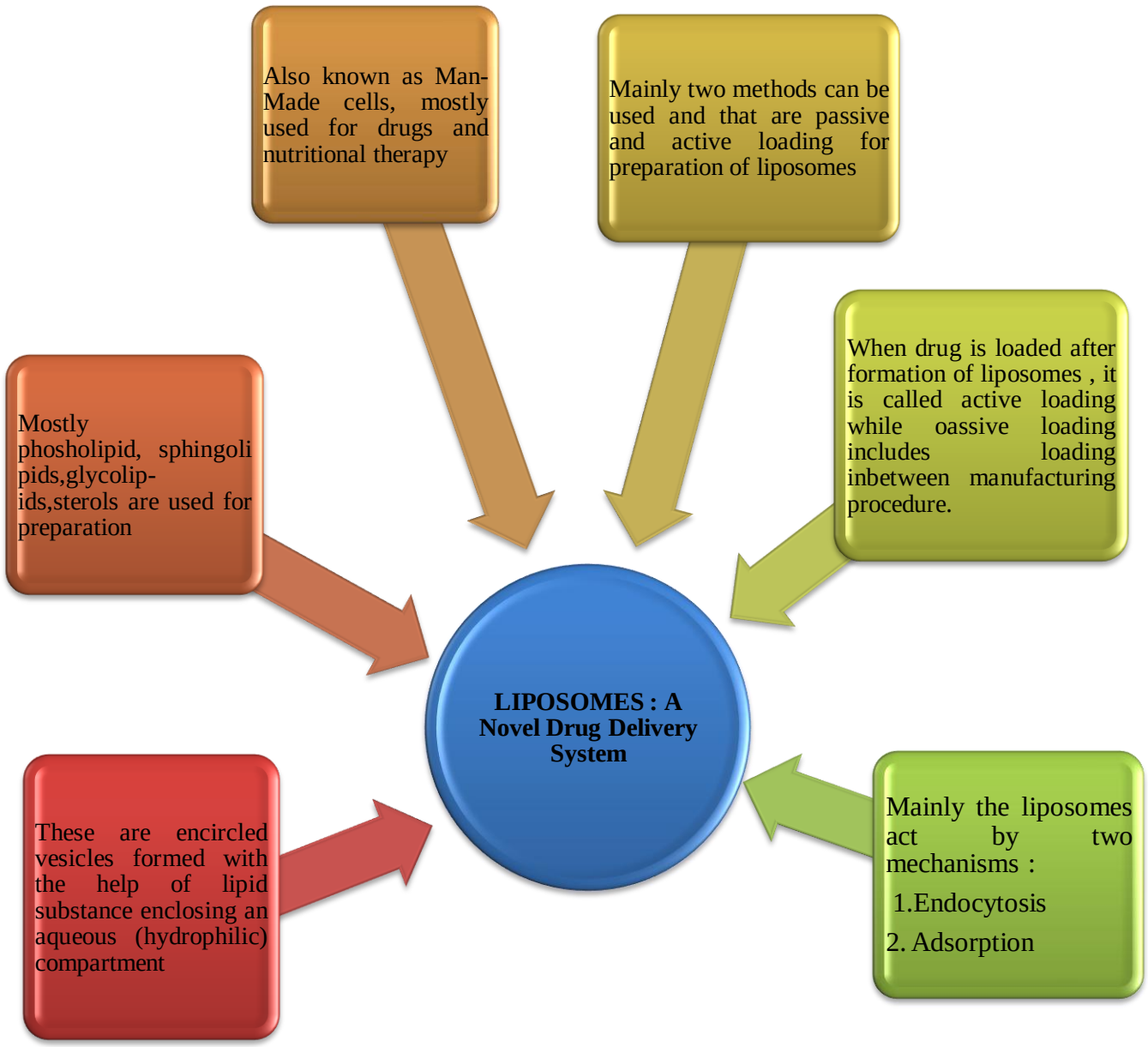


Figure 1 : Description about liposomes [17]

Various therapeutic and immunological applications of liposomes:-Liposomes are having different applications which are discussed in detail Figure 2 below [18].

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

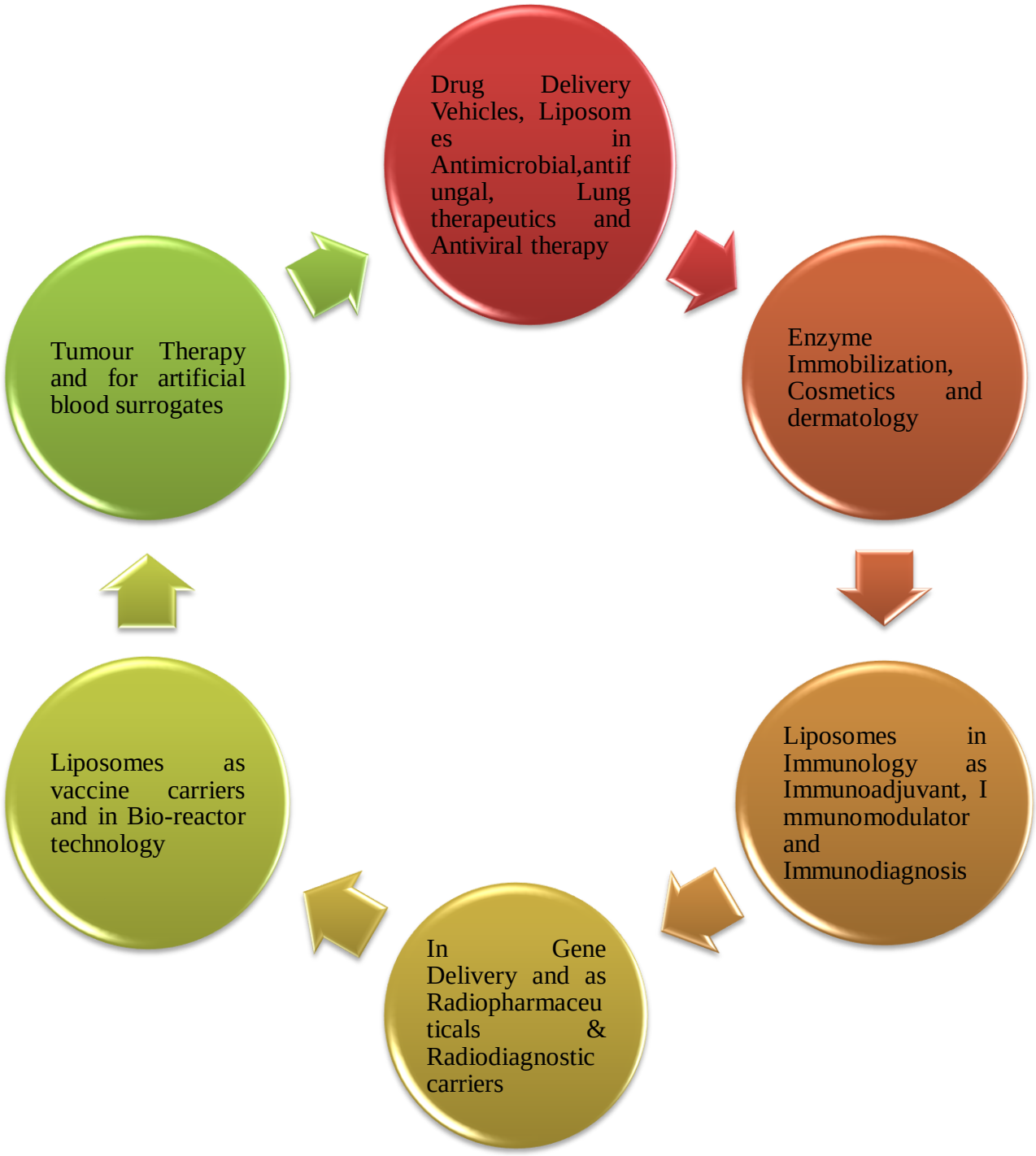
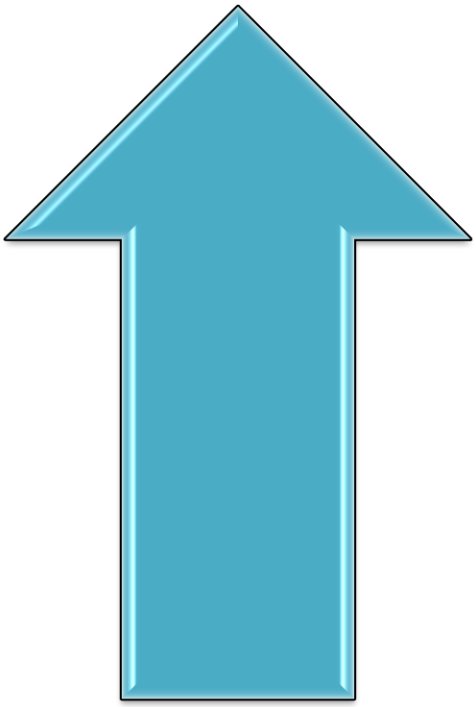


Figure 2: Applications of Liposomes

Merits and de-merits of liposomes:-Various merits and de-merits are discussed in Figure 3 [19, 20].

ISSN: 0971-1260
Vol-22-Issue-17-September-2019



MERITS

1. Elevated bioavailability as well as absorption.

2. Noninvasive.

3. Reduces pain as well as discomfort related with injections. Additionally lowers the chnaces of contamination.

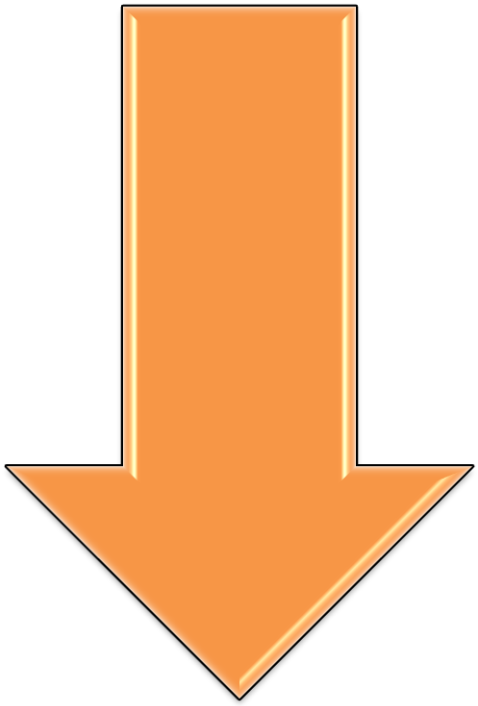
4. Encapsulation protects the compund against the harsh environment of the GI tract.

5.Enhanced intracellular delivery

6.It can be used for both hydrophilic as well as hydrophobic materials.

7.Dose can be adjusted for paediatrics and Geriatrics patients.

8. Proved to be Cost effective when lower dose of drug is administered .



DE-MERITS

1. Manufaturing cost is too high.

2. Stability is less.

3. Poor Manufactured products.

4. Enhanced intracellular delivery.

Figure 3: Merits and de-merits of liposomes

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

THIN FILM HYDRATION METHOD: This method was used to prepare curcumin loaded liposomes. Different steps have been discussed in Figure 4 below [21].

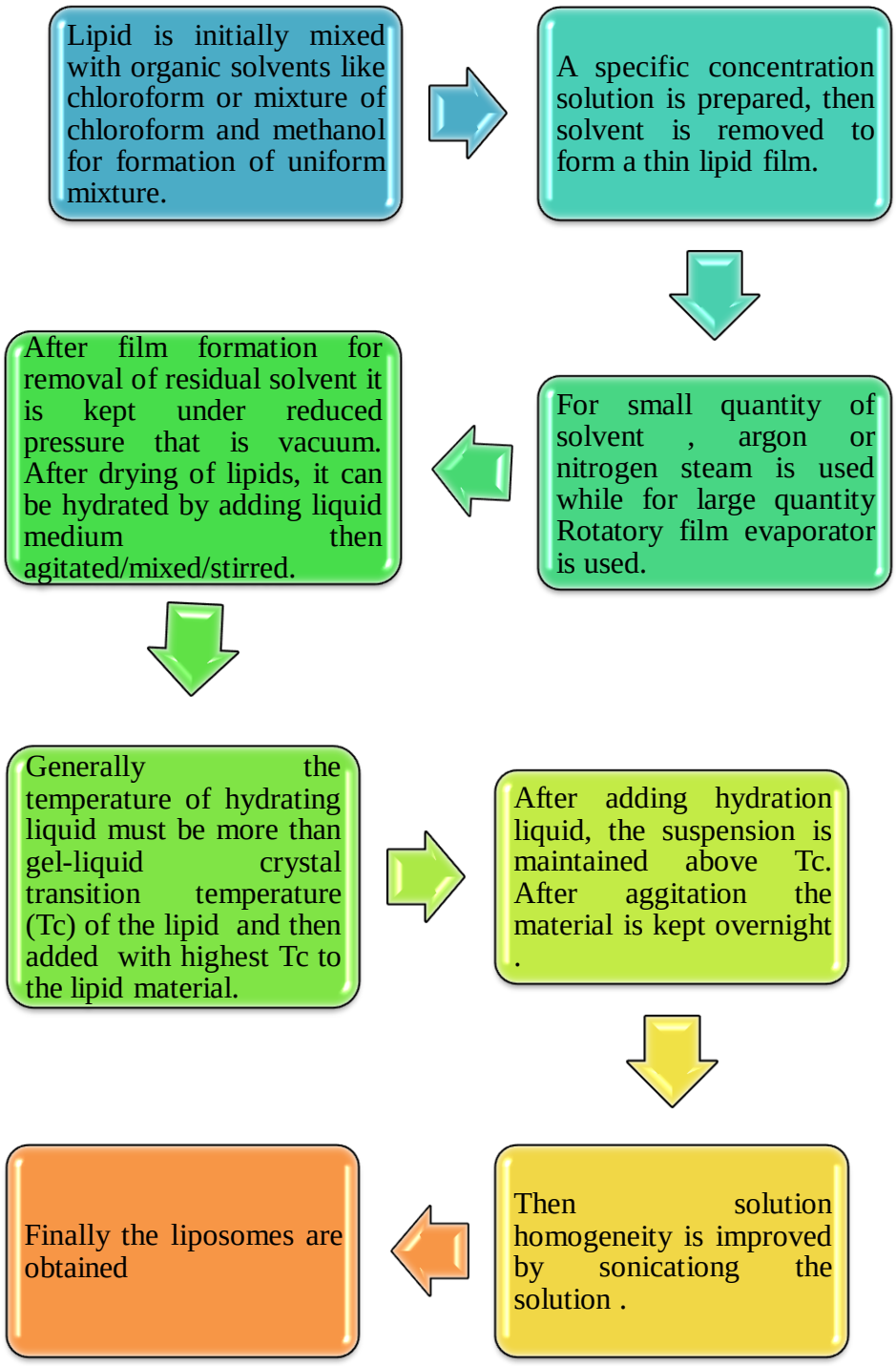


Figure 4: Brief about Thin film hydration me

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

CHARACTERIZATION OF LIPOSOMES-

Selection of Drug (Curcumin) and Phospholipid ratio:-To select drug and phospholipid ratio different formulation such as CP_1, CP_2, CP_3, and CP_4 was prepared as shown in Table 2 below and stability was checked up to 24 hrs [22].

Table 2: Drug (Curcumin) and Phospholipid ratio

FORMULATION CODE	DRUG:PHOSPHOLIPID RATIO	DRUG (mg)	PHOSPHOLIPID (mg)	OBSERVATION
CP_1	1:0.5	100	50	Settled down
CP_2	1:1	**100**	**100**	**Not settled down**
CP_3	1:1.5	100	150	Settled down
CP_4	1:2	100	200	Settled down

Formulation CP_2 having Drug (Curcumin) and Phospholipid ratio 1:1 molecular weight was selected on the basis of physical stability and visual observation.

Optimization of Phospholipid to cholesterol ratio:- Formulation CP_2 having Drug (Curcumin) and Phospholipid ratio 1:1 molecular weight was selected. Curcumin (100 mg) is used in each formulation. Ratio of Phospholipid to cholesterol varies as shown in observation Table 3 below. Formulation $CP2C_3$ having Drug (Curcumin) and Phospholipid ratio 1:1 molecular weight and phospholipid and cholesterol ratio 7:3 was selected on the basis of physical stability and microscopy [23, 24].

Table 3: Optimization of Drug (Curcumin), Phospholipid and Cholesterol ratio

FORMULATION CODE	DRUG:PHOSPHOLIPID RATIO	DRUG (mg)	PHOSPHOLIPID (mg)	Cholesterol (mg)	OBSERVATION (Microscopy)
$CP2C_1$	1:1	100	50	50	Lump formation
$CP2C_2$	1:1	100	60	40	Irregular vesicle formation

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

$CP2C_3$	1:1	**100**	**70**	**30**	Uniform vesicles formed
CP_2C_4	1:1	100	80	20	Irregular vesicle formation
CP_2C_5	1:1	100	90	10	Very less population of vesicles observed

Effect of Variables on Formulation (CP_2C_3):- Different variables have been selected to check their effect on the selected variables. Results have been discussed in Table 4 below.

- **Temperature: 50°C and 100°C -** 50°C temperature was suitable for formulation as no deterioration was observed at that temperature.
- **RPM: 50 rpm and 100 rpm –** At 100 rpm vesicles formed was uniform in shape ans size.
- **Hydration Media: Water and PBS7.4 –** No significant effect was observed. Hence, Water was used.
- **Sonication (Bath): 15 minutes and 30 minutes --** No significant effect was observed. Hence, 15 min sonication time was selected [25, 26].

Table 4: Effect of variables on formulation

Formulation Code	**15min Sonication**	**30min Sonication**	**Observation**
CP_2C_3	✓	✓	**No significant effect was observed. Hence, 15 min sonication time was selected.**
Formulation Code	**Water**	**PBS7.4**	**Observation**
CP_2C_3	✓	✓	**No significant effect was observed. Hence, Water was used.**
Formulation Code	**50 RPM**	**100 RPM**	**Observation**
CP_2C_3	--	✓	**At 100 rpm vesicles formed was uniform in shape ans size.**
Formulation Code	**50°C**	**100°C**	**Observation**
CP_2C_3	✓	--	**50°C Temperature was suitable for formulation as no deterioration was observed at that temperature.**

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

Stability Study: Stability has been checked for 0 day to 14 day. Results have been shown in Table 5 below. It was observed that the final formulation was stable upto 14 days in refrigerator as compared to room temperature and pH was same during this period i.e. 6.4 [27, 28].

Table 5: Stability study observation

At Room temperature					
Formulation Code	**0 day**	**7th Day**	**14th day**	**Microscopy**	**pH**
CP_2C_3	**Stable**	**Stable**	**Unstable**	**Lumps are formed by 14th day**	**6.2**-0 day **6.2**-7th Day **6.5**-14th day
In refrigeration					
Formulation Code	**0 day**	**7th Day**	**14th day**	**Microscopy**	**pH**
CP_2C_3	**Stable**	**Stable**	**Stable**	**Uniform vesicles are observed for all days**	**6.4** for all days

CONCLUSION

Curcumin (Turmeric) is an ancient plant used medicinally from many decades. **"Indian Saffron"** is another name of Turmeric. Also known as "Haldi" in North India and "Manjal" in south India. About 100 components have been isolated and main constituent is volatile oil having turmerone and other coloring agents which is curcuminoids. Curcumin shows useful effects on a number of ocular diseases, such as Iris iritis, Glaucoma, Diabetic retinopathy, Cataract, AMD, Dry eye etc. And also it can used to treat number of diseases like Osteoporosis, Diabetes, Hypertension, Chronic Kidney disease etc.

Liposome can be used to entrapped and entangled hydrophilic drugs in aqueous (liquid) compartment while hydrophobic drugs can be incorporated in lipid phase. Liposomes can be prepared by conventional as well as novel techniques. The literature reports suggested that liposomes of curcumin are prepared for oral administration as well as for topical preparation for

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

various diseases as well for beauty enhancement. But there are very less marketed preparation available in market of curcumin for eye diseases.

So the main aim of this study was to make a formulation of curcumin which can be useful in treatment of various eye diseases like dry eye, cataract etc. At the end, liposomes of curcumin was prepared and their stability study was done.

References

1. Waugh A, Grant A. The Special Senses. Ross and Wilson anatomy and physiology, Philadelphia, Churchill Livinstone, Elsevier. 2006; 194-204.
2. Snell RS, Lemp MA. The Eyeball. Clinical Anatomy of The Eye. 2013; 132-213.
3. Tortora G, Grabowski SR. The Special Senses. Principles of Anatomy and Physiology, Hoboken, New Jersey, John wiley & sons.2003; 531-545
4. Purves D, Augustine GJ, Fitzpatrick D, Katz LC, LaMantia AC, McNamara JA, Williams MA. Vision: The Eye. Neuroscience. 2001. ISBN-10: 0-87893-742-0
5. Shahsuvaryan ML, Ohanesian RV. Anatomy and Physiology of Eye. Eye Diseases. 2005; 1-3.
6. Tarr JM, Kaul K, Chopra M, Kohner EM, Chibber R. Pathophysiology of Diabetic Retionpathy. ISRN Ophthalmology. 2013; 1-3.
7. Zhang J, Tuo J, Wang Z, Zhu A, Machalińska A, Long Q. Pathogenesis of common ocular diseases. Journal of Ophthalmology. 2015; 1-2.
8. Nowak JZ. Age-related macular degeneration (AMD): pathogenesis and therapy. Pharmacological Reports. 2006; 58(3): 353-363.
9. Gaudana R, Jwala J, Boddu SHS, Mitra AK. Recent Perspectives in Ocular Drug Delivery. Pharmaceutical Research.2008; 26 (5): 1197-1216.
10. Tripathi,KD.Anti Adrenergic drugs and drugs for Glaucoma. Essential of Medical Pharmacology. New Delhi: Jaypee Brothers Medical Publishers. 2015:.151-157.
11. Wong D, Albietz JM, Tran H, Yun T, Han J, Schmid KL. Treatment of contact lens related dry eye with antibacterial honey. Contact Lens and Anterior Eye. 2017; 40 (6):389-393.
12. Galor A, RezaMoein H, Lee C, Rodriguez A, Felix ER, Sarantopoulos KD, Levitt RC, Neuropathic pain and dry eye. The Ocular Surface. 2017; 16 (1): 31-44.
13. Benzie IFF, Wachtel-Galor S. (Eds), Turmeric, the Golden spice. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis, 2011, Chapter 13.

ISSN: 0971-1260
Vol-22-Issue-17-September-2019

14. Kumar SSD, Houreld NN, Abrahamse H. Therapeutic Potential and Recent Advances of Curcumin in the Treatment of Aging-Associated Diseases. MDPI-Molecules. 2018; 23(4):835.

15. Peddada KV, Brown A, Verma V, Nebbioso M. Therapeutic Potential of curcumin in major retinal pathologies. PubMed. 2019; 39(3):725-734

16. PescosolidoN,GiannottiR,PlaterotiAM,PascarellaA,NebbiosoM.Curcumin:Therapeuti cal Potential in Ophthalmology. Plant Medica. 2013; 80(4).

17. Kazazis C, Vallianou NG, Kollas A, Evangelopoulos A. Curcumin and Diabetes: Mechanism of action and its Anti-Diabetic Properties. Current Topics in Nutaceuticals Research. 2014; 12(4):135-142.

18. Hewlings S, Kalman DS. Curcumin: A Review of Its' Effects on Human Health. MDPI-Food.2017; 6 (10):92.

19. Rathaur P, Raja W, Ramteke PW, John SA. Turmeric: The Golden Spice of Life. International Journal of Pharmaceutical Sciences and Research. 2012; 3(7): 1987-94.

20. Ashrafi Kooshk MR, Mansouri K, Mostafanadi M, Khodarahmi S, Khodarahmi R. In vitro anti-cancer activity of native curcumin and "Protein-Curcumin" systems: A perspective on drug-delivery application. Journal of Reports in Pharmaceutical Sciences. 2013; 2(1): 66-74.

21. DavisBM,PahlitzschM,GuoL,BalendraS,ShahP,RavindranN,MalaguarneraG,SisaC,Sha msher E, Hamze H, Noor A, Sornsute A, Somavarapu S, Cordeiro MF. Topical Curcumin Nanocarriers are Neuroprotective in Eye Disease. Nature Research Journal.2018;8.

22. Mirzaeei S, Alizadeh M. Design and evaluation of soluble ocular inserts for controlled release of chloramphenicol. Journal of Reports in Pharmaceutical Sciences. 2017; 6 (2):123-133.

23. Mehta RM. Ophthalmic products. Dispensing Pharmacy. Delhi: Vallabh Prakashan. 2012; 296-315.

24. Baranowski P, Karolewicz B, Gajda M, Pluta, J. Ophthalmic Drug Dosage Forms: Characterisation and Research Methods. The Scientific world journal. 2014; 1-14.

25. Bhrahmankar DM, Jaiswal SB. Controlled Release Medication. Biopharmaceutics and Pharmacokinetics- A Treatise, New Delhi: Vallabh Prakshan, 2008.360-362.

26. Lachman L, Lieberman HA, Kanig JL. Novel drug delivery system .In R.K.Khar., S.P.Vyas., F.J.Ahmad.,& G.K.Jain (Eds.). The theory and practice of industrial pharmacy. Philadelphia: Lea & Febiger. 1976; 883-885.

27. Tripathi KD. Anti Adrenergic drugs and drugs for Glaucoma. Essential of Medical Pharmacology. New Delhi, Jaypee Brothers Medical Publisher. 2015; 151-157.

28. Wadhwa S, Paliwa R, Paliwal SR, Vyas SP. Nanocarriers in ocular drug delivery: an update review**.** Current Pharmaceutical Design**.** 2009; 15(23):2724-50