CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2652057

Available online at: http://www.iajps.com Research Article

PREPARATION AND EVALUATION OF TAPENTADOL *INSITU* GEL

Dr. T. Mangilal*, S.Likitha, Shaistha Tabassum, Syeda Sana Fatima, S.Nikitha
Geethanjali College of Pharmacy, Cheeryal (V), Keesara (M), Medchal (Dist), Telangana State.501301.

Article Received: February 2019 **Accepted:** March 2019 **Published:** April 2019

Abstract:
The aim of the present study is to prepare and evaluate Tapentadol insitu gel. In the present study, an attempt was made to prepare topical analgesics gels by hydrogel/ Dispersion method by using polymer Carbopol 940 as a key ingredient which gives pH-induced sol to gel conversion of the formulations. Different formulations were prepared by varying the ratios of carbopol 940 and different grades of Hydroxyl Propyl Methyl Cellulose (HPMC K100, HPMC K4M). These formulations were evaluated for parameters like pH, drug content, viscosity, gel strength, in vitro drug release and drug excipient compatibility. In this study, the release profile depends on the concentration of carbopol 940 and grade HPMC. The gel was stable during stability studies according to ICH guidelines 30±20 C / 65±5% RH and 40± 20C / 75±5% RH for two months. It shown emollient, analgesic action on application to the skin, diffuses directly in to the systemic circulation and shows immediate action. This formulation does not show any redness, edema, inflammation and irritation on the site of application. Hence it was concluded that the gels without side effects having analgesic property can be used as provision of barrier to protect the skin. So the formulation is safe to use.

Key Words: *Tapentadol, Carbopol, HPMC K100, HPMC K4M,Topical analgesics gel.*

Corresponding author:
Dr.T.Mangilal,
Professor and Head.Department of Pharmaceutics,
Geethanjali College of Pharmacy, Cheeryal,Keesara,
Medchal Malkajgiri-50301, Telangana State, INDIA.
Email.Id: teelavath@gmail.com, Mobile: 8008241585.

QR code

Please cite this article in press T.Mangilal et al., **Preparation and Evaluation of Tapentadol *Insitu* Gel.,** *Indo Am. J. P. Sci, 2019; 06(04).*

INTRODUCTION:

A gel is a solid jelly-like soft material that can have properties ranging from soft and weak to hard and tough. Gels are defined as a substantially dilute cross-linked system[1], which exhibits no flow when in the steady-state. By weight, gels are mostly liquid, yet they behave like solids due to a three-dimensional cross-linked network within the liquid. It is the cross linking within the fluid that gives a gel its structure (hardness) and contributes to the adhesive stick (tack). In this way gels are a dispersion of molecules of a liquid within a solid in which liquid particles are dispersed in the solid medium . The word *gel* was coined by 19th-century Scottish chemist Thomas Graham .

Uses:

- Glyco gelatin gels are used as medicated pestilles
- Uses in gel filtration aero gels.
- Used in hard and soft gel capsules.
- Gelatine gels used as solid media for culture preparation. Economical use of gel as paint.
- Many substances can from gels when a suitable thickener or gelling agent is added to their formula. This approach is common in manufacture of wide range of products, from foods and paints, adhesives.
- In fibre optics communications, a soft gel resembling “hair gel” in viscosity is used to fill the plastic tubes containing the fibers,.the main purpose of gel is to prevent water instrusion if the buffer tube is breached, but the gel also buffers the fibres against mechanical damage when the tube is bent around corners during installation, or flexed. Additionally gel act as a processing aid when the cable is being constructed, keeping the fibers central whilst the tube material is extruded around it[2].

Advantages of gels :

- Gels are used to achieve optimal cutaneous and percutaneous drug delivery.
- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH.
- Gels are having property to avoid enzymatic activity and drug interaction with food and drinks.
- They can substitute for oral administration of medication when the route is unsuitable.
- They can avoid the first pass effect, that is, the initial pass of drug substance through the human body.
- They avoid systemic and portal circulation following gastrointestinal absorption.
- Gels are not deactivated by liver enzymes because the liver is bypassed.
- They are non-invasive and have patient compliance.
- They are applied over skin for slow and prolonged absorption.
- Gels have also been applied in pharmacy to some viscous suspension for oral use for example Aluminum hydroxide gel.
- They have localized effect with minimum side effects.

Disadvantages of gels:

- Gels have possibility of allergenic reactions.
- Enzyme in epidermis may denature the drugs of gels.
- Drugs of larger particle size do not absorb through the skin.
- They have poor permeability of some drugs through the skin.
- Selection of area to be examined carefully during application of gels.
- Gels which are used for the introduction into body cavity or the eyes should be sterilized.
- They may causes application side reactions.
- They may cause skin allergy during application

Classification Of Gels: Gels are classified in two ways: on the basis of continuous phase, and on the basis of nature of bond involved in 3 dimensional solid networks[3].

Types of gels:

A) Based on continuous phase.

B) Based on nature of bond.

A) Based on continuous phase

1. Organogel
2. Hydrogels
3. Xerogels

Organo gels: Solid material composed of liquid organic phase entrapped in three dimensional cross linked network. Non crystalline, non greasy, thermoplastic. Used in pharmaceutical industry,cosmatics,food. Sorbitan monostearate, a hydrophobic nonionic surfactant, and numbers of organic solvents such as hexadecane, isopropyl

myristate, and a range of vegetable oils are present. Gelation is achieved by dissolving/dispersing the organo gelator in hot solvent to produce an organic solution/dispersion, which, on cooling sets to the gel state. Such organogels are affected by the presence of additives such as the hydrophilic surfactant, polysorbate 20, which improves gel stability and alters the gel microstructure from a network of individual tubules to star-shaped "clusters" of tubules in the liquid continuous phase. Another solid monoester in the sorbitan ester family, sorbitan monopalmitate, also gels organic solvents to give opaque, thermo reversible semisolids. Like sorbitan monostearate gels, the microstructure of the palmitate gels comprises an interconnected network of rod like tubules[4].

Hydrogels: These are network of polymer chains that are hydrophilic or colloidal gel in which water is an dispensing medium. High absorbent, degree of flexibility. Used as environment sensitivity detector, used in contact lenses, used as scaffolds in tissue engineering, used in ecg medical electrode, used as glue in sustained released tdds. It also provides absorption and debriding.

Xerogels: Gels in which vehicles has been removed, leaving a polymer network (e.g.)Polymer flim. Used in drug delivery system.

Preparation Of Gels:

Gels are normally in the industrial scale prepared under room temperature. However few of polymers need special treatment before processing. Gels can be prepared by following methods.[5-6]

1. Thermal changes
2. Flocculation
3. Chemical reaction

1) Thermal changes: solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reducing, the degree of hydration is reduced and gelatin occurs. (Cooling of a concentrated hot solution will produce a gel). E.g.: - gelatin, agar sodium oleate, guar gummed and cellulose derivatives etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method.

2) Flocculation: here gelation is produced by adding just sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitant. E.g.: solution of ethyl cellulose, polystyrene in benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether. The addition of salts to hydrophobic solution brings about coagulation and gelation is rarely observed. The gels formed by flocculation method are thixotropic in behavior. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is to “salt out”, the colloidal and gel

3) Chemical reaction: in this method gel is produced by chemical inter action between the solute and solvent. E.g.: aluminum hydroxide gel can be prepared by interaction in aqueous solution of an aluminum salt and sodium carbonate an increased concentration of reactants will produce a gel structure. Few other examples that involve chemical reaction between pva, cyanoacrylates with glycidol ether (glycidol), toluene diisocyanates (tdi), methane diphenyl isocyanine (mdi) that cross-links the polymeric chain lation doesn’t occur.

Method Of Preparation[7-9]

Fusion method: In this method various waxy materials employed as gallant. In non polar media. Drug was added when waxy materials melted by fusion stirred slowly until uniform gel formed.

Cold method: Water was cooled to 4-10c placed it in mixing container gelling agent was slowly added and agitating until solution is complete maintained temperature below 10c. drug was added in solution from slowly with gentle mixing. Immediately transfer to container and allow.

Dispersion method: Gelling agent was dispersed in water with stirring at 1200rpm for 30 minutes. Drug was dissolved non aqueous solvent with preservative. This solution was added in above gel with continuous stirring.

B) Based on nature of bond:

Based on nature of bond involved in three dimensional solid network, dispensed solid, hydrophilic polymer, type1 type2

Dispersed solids: This undergoes flocculation. The nature of interaction between particles in network may be Vander walls or electrostatics interaction.

Examples; Al-hydroxide gel USP ,kaoline.

Hydrophilic Polymers: Hydrophilic polymers are dispensed with in aqueous phase.

Type 1: Irreversible system with three dimensional network formed by a co-valent bonds between micro molecules.

Example: network is formed by polymerization of monomers of its.

Type 2: Reversible system in which interaction occurred between polymers by a hydrogen bonding temporary destruction of bonds when stress applied thus formulation enable to flow.

Formulation Of Gels:

Antioxidant: It Prevents or slows oxidation of other components.

Examples: Tocopherol, butylated hydroxyl toluene, or a reducing agent such as ascorbic acid.

Base: Bases act as vehicles to deliver the drug and to impart emollient and lubricant properties to the preparation.

Examples: petrolatum, white petrolatum yellow and white ointment or mineral oil and, lanolin, cholesterol.

Buffer: Acid-conjugate base mixture employed to control pH and therefore control ionization state of drug and impart stability.

Example: citrate buffer, phosphate buffer, tartarate buffer[11]

Chelating agent: It has the ability to bind metal ions; prevents auto-oxidation phenomenon frequently catalyzed by metal ion and enhances the action of preservatives by iron and copper ions essentially to microbial growth.

Examples: EDTA, citric acid.

Emulsifying agent: Emulsifying agent helps in reducing the surface tension of two phases in an emulsion, preventing coalescence of individual phases.[12]

Examples: detergent, emulsifying wax (detergent-treated wax) , cetostearyl alcohol, polysorbate 20.

Humectants: It promotes the retention of water in a mixture.

Examples: glycerin, propylene glycol, polyethylene glycol (low molecular weight).

Permeation enhancer: Permeation enhancer facilitates diffusion process of active ingredient across the stratum corneum by chemical modification.[13]

Examples: ethanol, oleic acid, propylene glycol, polyethylene glycol (400).

Preservative: It prevents or slows the microbial growth; may be one of four major compound types: acid, alcohol, quaternary ammonium compounds or organic mercurial.[14]

Examples:

Acid: benzoic acid;

Alcohol: phenyl ethyl alcohol;

Quaternary ammonium: stearyl dimethyl benzyl ammonium chloride;

Organic mercurial's: thimerosal

Thickening agents: It increases the viscosity of semisolid preparation. They may be derived from natural, semi synthetic or synthetic sources.[15]

Examples:

Natural: cellulose, pectin;

Semi synthetic: methyl cellulose (sodium);

Synthetic: carbopol

Fragrances: It gives agreeable odor to the formulation.

Examples: lavender oil rose oil, almond oil, lemon oil .

MATERIALS AND METHODS:

Materials

Tapentadol procured as a gift sample from MSN Organics Pvt Ltd. Bibinagar, Telangana, India, HPMC K4M, HPMC K100 purchased from Merck Specialities Pvt Ltd, Mumbai, India, Carbapol 940 purchased from Qualikem Pvt Ltd, India and all reagents are used in the laboratory are laboratory grades.

Methods

The Tapentadol along with Polymers formulated in three different ratios into in situ gel by Dispersion method.

TABLE-1 FORMULATION CHART

METHODS	Dispersion method					
FORMULATIONS	F1	F2	F3	F4	F5	F6
CONCENTRATIONS	1:25	1.50	1.75	1:25	1.50	1.75
Tapentadol	200mg	200mg	200mg	200mg	200mg	200mg
Carbopol 940	50mg	50mg	50mg	50mg	50mg	50mg
HPMC K100	25mg	50mg	75mg	---	---	---
HPMC K4M	---	---	---	25mg	50mg	75mg
Methyl Parabin	05mg	05mg	05mg	05mg	05mg	05mg
Distill Water	qs	qs	qs	qs	qs	qs

PREPARATION OF *in situ* GELS [16-20]

- Formulations were prepared by dispersion method carbopol 940 as pH-dependent *in situ* gelling agent and HPMC as gel-strengthening agent dissolved in distilled water as per the required quantity with continuous stirring until completely dissolved and allowed to hydrate overnight.
- After complete hydration of polymers, tapentadol was added to the mixture. The resultant solution was thoroughly mixed.
- Another excipient like Methyl parabbin was added as a preservative to the above solution and mixing was confirmed until uniform and clear solutions were formed. Final volume was made by adding required amount of distilled water.

RESULTS AND DISCUSSION:

Calibration curve values

The absorbance was measured in a UV spectrophotometer at 228nm against 7.4 pH buffer. The absorbance so obtained were tabulated as in table 2.Calibration curve was plotted and shown in figure 1 and regression value R^2 of 0.999 was obtained.

TABLE 2: CALIBRATION CURVE VALUES

S.No	Conc µg/ml	Absorbance
1	0	0
2	2.0	0.061
3	4.0	0.119
4	6.0	0.179
5	8.0	0.240
6	1.0	0.310

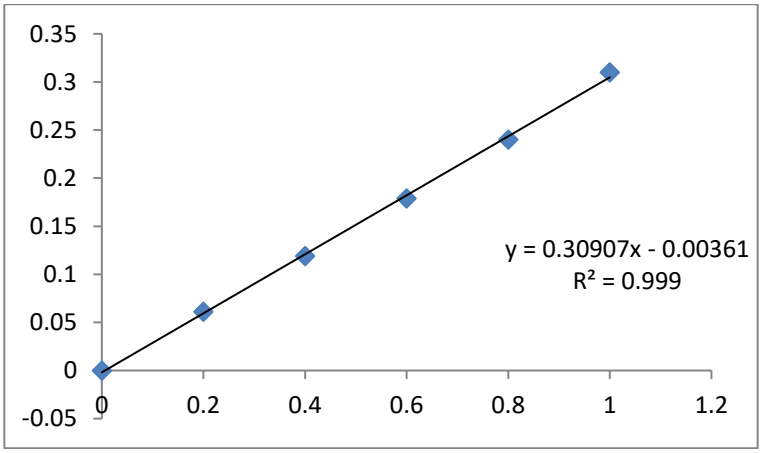

Figure 1 Standard graph of Tapentadol in 0.1N HCl

The gel is evaluated for the following physical parameters

Organoleptic characteristics: The formulation is tested for physical appearance, texture, homogenecity, phase separation and color. The above characteristics were evaluated by visual observation and inference given as following.

- **Physical appearance:** It is a semisolid preparation and opaque in nature as shown in table 3.
- **Color:** White/Gel in color as shown in table 3.

- **Odour:** Slight characteristic odour is observed as shown in table 3.
- **Phase separation:** The formulated gel is kept in a closed container at 25-30ºc not exposed to light. Phase separation was observed carefully every 24 hours for 30 days. There is no change in phase separation was observed as shown in table 3.
- **Texture and homogenecity:** A small amount of formulated gel is pressed in between thumb and index finger to check the homogenecity of the gel and also immediate skin feel including stiffness, greasiness as shown in table 3.
- **Presence of foreign particles/grittiness:** A small amount of gel was spread on glass slide free from grease and then observed against diffused light and it was found that there is no presence of foreign particles as shown in table 3.
- **Appearance:** The formulation was kept for long period of time, it was found that there is no change in Organoleptic properties of gel. as shown in table 3.

TABLE 3. ORGANOLEPTIC STUDIES

S.NO.	CHARACTERS	OBSERVATION
1.	Physical Appearence	Semi-solid
2.	Color	White/Gel
3.	Odor	Characteristic
4	Phase separation	No phase separation have been observed.
5.	Presence of foreign particles	Absent
6.	Texture and homogenecity	Good
7.	Appearance	No change in Organoleptic properties in gel

pH: pH of the gel is determined by using digital pH meter. About 1 g of the gel was weighed and dissolved in 100 ml of distilled water and stored for 2 hours. The measurement of pH of each formulation was done and calculate average values. The pH of the gel was found to be 6.2, which is suitable for the skin pH.

TABLE 4. PH VALUES

S.NO	pH
1	5.8
2	6.5
3	6.2
4	6.4
Average	6.2

Viscosity: Viscosity of the gel is determined by Brookfield viscometer II + model using spindle no.64 SLV-4 at a temperature of 25ºc and determination were carried out and the average of three readings were recorded. viscosity of the gel was found to be 7.7Cps, which indicates that the gel is easily spreadable by small amounts of shear.

TABLE 5. VISCOSITY VALUES

S.NO.	Viscosity (Cps)
1	10
2	7
3	7
4	7
Average	7.7

Moisture absorption studies: About 50 mg of gel was taken on a watch glass. A beaker is taken with full of water and kept in a desiccator without adsorbent and to get saturated. Watch glass with gel is introduced into desiccator. It was left for 24 hrs.

Microbial Test: When formulation was tested for growth of microbes, it was found that there is no growth of microbes within the prescribed limits. So these formulation are safe to use for skin.

TABLE 6. RESULTS OF MICROBIAL TEST

Microbial load	Limits	Results
TMC	NMT 100	65
Limit tests : E.Coli, S.aureus, Solmonella	No Characteristic colonies	complies

Spreadability: It determines the extent to which the formulation is readily spreads on application to skin. The bioavailability efficiency of a formulation also depends on its spreading value. It was expressed in terms of time in seconds taken by two slides to slip off from the gel, placed in between the slides, under certain load. Lesser is the time taken for separation of the two slides, better the spreadability. Two glass slides of standard dimensions were taken. The gel was applied between the glass slides and they were pressed together to obtain a film of uniform thickness. Weights are gradually added in increasing order to the upper slide by means of string and hook. Note the time at which the upper slide moves over the lower plate to cover a distance of 10 cm. The spreadability (s) can be calculated using the formula S=M.L/T where,

M= weighed tied to upper slide

L= length of glass slide

T=time taken to separate the slides

TABLE 7. SPREADABILITY VALUES

S.no.	Time in Seconds	Spreadablity(in grams)
1.	10	13.6
2.	10	13.6
3.	9	15
4.	8	18
Average		15.05

Stability studies: stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess the drug and formulation stability, stability studies were done according to ICH guidelines. The gel is filled in a bottle and then it is kept in humidity chamber maintained at 30 ± 2^0 C / 65±5% RH and 40 ± 2^0C / 75±5% RH for two months. At the end of studies, samples were analysed for the physical properties and viscosity.

TABLE 8. STABILITY STUDIES

S.NO	pH	COLOUR	VISCOSITY
1	6.2	White	10
2	6.4	White	7
3	6.5	White	7
4	6.8	White	7

After feel: Emolliency, slipperiness and amount of residue left after the application of fixed amount of gel was found good

Removal: The ease of removal of gel applied was examined by washing the applied part with tap water.

Irritancy test: Mark an area (1sq cm)on the left dorsal surface of mice paw. The gel was applied to the specified area and time was noted. Irritancy, erythematic, edema was checked if any for regular intervals up to 24hours and reported. The formulation shows no redness, edema, inflammation and irritation after applying on the skin. Hence, this formulation is safe to use for skin.

TABLE-8: ALL EVALUATION STUDIES

S.NO.	TEST	RESULT
1.	pH	6.2
2.	Viscosity	7.7Cps
3.	Spreadability	15.05
4	Microbial Test	No growth of micro organisms
5.	Stability studies	Stable
6.	After feel	Good
7.	Removal	Easily removed
8.	Irritancy	Absent

Incompatibility Studies:

Drug excipients interaction study:

Drug excipients' interactions play a vital role in the release of the drug from the formulation. The pure Tapentadol and its mixture with each of different concentrations of HPMC and carbopol 940 were scanned over a range of 400-4500 cm^{-1} using FTIR instrument (FTIR- 1700, Shimadzu, Kyoto, Japan). The drug exhibits peaks due to ketonic group, broad peak of alcohol group and C=C stretching which is shown in Figure 2. It was observed that there were no changes in these main peaks in the IR spectra of a mixture of drug and polymers [Figures 3]. The FTIR study revealed no physical or chemical interactions of Tapentadol with HPMC and carbopol 940 as evident.

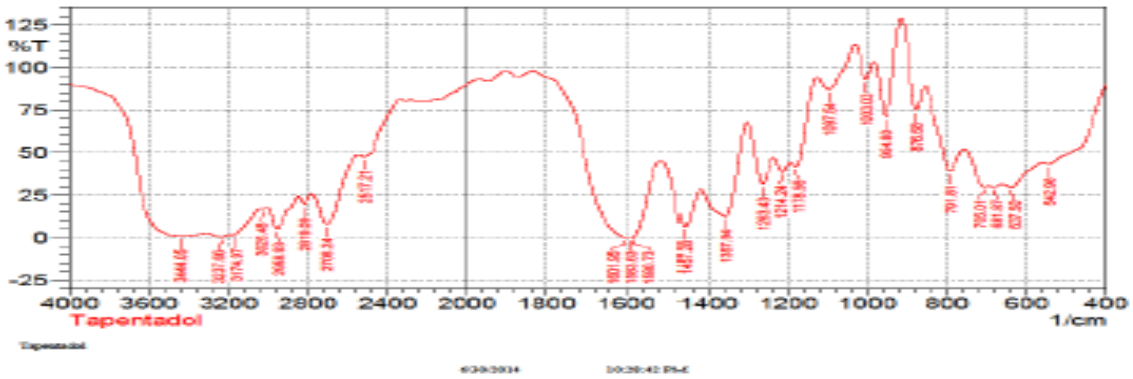

Figure 2.FTIR of Tapentadol

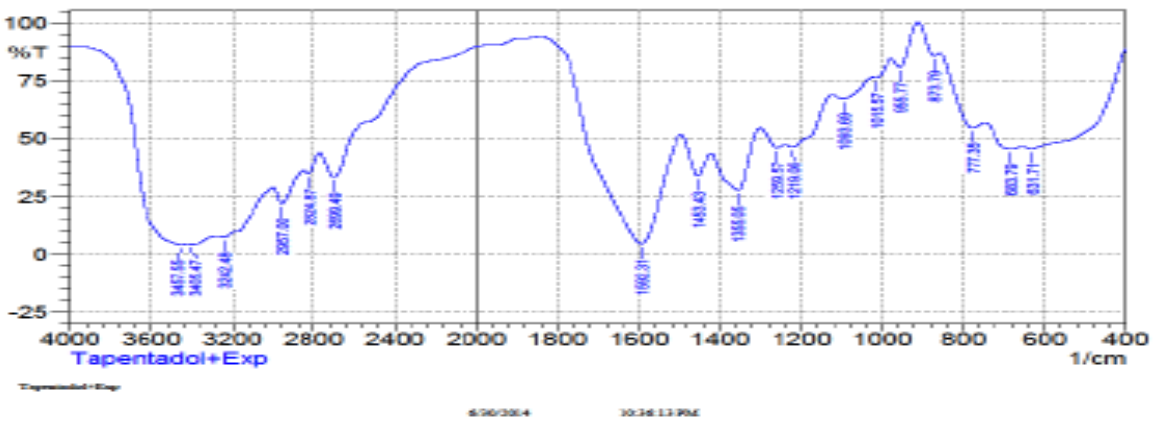

Figure 3.FTIR of Tapentadol and Excipients

CONCLUSION:

- From the results it is concluded that the formulated Tapentadol analgesic gel is safe to use for topical application.
- In general analgesics are administered in the form of parentals, through oral route or rectal route. While administration in the form of a gel is observed rarely.
- In this regard we formulated a gel using Tapentadol as an active ingredient, using the different ratios of carbopol 940 and different grades of Hydroxyl Propyl Methyl Cellulose (HPMC K100, HPMC K4M).The formulated gel has been subjected to all the possible evaluation tests and the results obtained were within the standard limits.
- Further research will carry out to check scientifically for the Pharmacological action of the selected formulation.
-

REFERENCES:

1. A.Sumiishikawa. An ionic liquid gel with ultra low concentrations of tetra-arm polymers-Gelation kinetics and mechanical and ion-conducting properties polymer. Journal of Pharma Science, 2018;166:38-43.
2. 2.Chaoyuan. Gelation of Konjac glucommanan compound gel. Journal of food Hydrocolloids ,2017; 87:158-164.
3. 3.Fengzheng. Voltammetric and electrosynthetic triggered gel formation. Electrochimica Acta, 2018; 296:1095-1101.
4. 4.Guan-haiwang. Electroactive polyaniline/silica hybrid gel: Controllable sol-gel transition adjusted by chitosan derivatives carbohydrate Polymers. International Journal of Pharmaceutical Technology Research, 2018; 202:523-529.
5. 5.Hatsuemoritaka. Effects of the gel size before ingestion and agarose molecular weight on the textural properties of a gel bolus. Journal of food Hydrocolloids, 2017; 89:892-900.
6. 6.Jinfengpeng. Mixed gels from whey protein isolate and cellulose microfibrils. International Journal of Biological Macromolecules, 2016; 124:1094-1105.
7. J. L. Zatz, J. P. Berry and D. A. Alderman. Dispersed Systems gels. International Journal of Pharamceutical Dosage forms, 2015; 2:495–510.
8. K. A. Fults and T. P. Johnston. Sustained-release of urease from a poloxamer gel matrix. Journal of Parental Science and Technology, 2015;44(2):58–65.
9. 9.L.Lyzamendoza.Nanocellulose for gel electrophoresis. Journal of Colloid and Interface Science, 2018;540:148-154.
10. M. Tsakala, J. Gillard, M. Roland, F. Chabot, and M. Vert. Pyrimethamine sustained release systems based on bioresorbable polyesters gel for chemoprophylaxis of rodent malaria. Journal of Controlled Release systems,2015;5:233–242.
11. 11.Nikolabosnjak. Modeling of fiber-reinforced polymeric gels. International Journal of Biological sciences, 2018;96:7-18.
12. 12.Priyadarshichakraborty. Conducting gels- A chronicle of technological advances progress in Polymer Science. International Journal of Biological sciences, 2019; 88:189-219.
13. 13.R. K. Chang, J. C. Price and C. W. Whitworth. Control of drug release rates through the use of mixtures of polycaprolactone and cellulose

propionate polymers gel. Pharm. Tech,2015; 10:24–33.
14. S.Raghunandan. Role of water in the sol-gel synthesis of atrium monosilicate Ceramics. International Journal of Pharmaceutical sciences, 2019;45(4):4487-4492.
15. 15.Tezarramdhana.Time dependent gelling properties of cuboid alginate gels made by external gelation. Journal of Food Hydrocolloids, 2018; 90:232-240.
16. 16.Toktamfarjami. An overview on preparation of emulsion-filled gels and emulsion particulate gels. Trends in Food Science & Technology,2018; 86:85-94.
17. 17.Viet T.N.T.bui. Mobility of carrageenan chains in iota- and kappa carrageenan gels colloids and Surfaces, Physicochemical and Engineering Aspects, 2015; 562:113-118.
18. 18.Y.Cha and C.G.Pitt. A one-week subdermal delivery system for L-methadone based on biodegradable gels. Jounal of. Controlled Release systems,2015;7:69–78.
19. 19.Yuezheng. Contact mechanics of a gel under constrained swelling agents.Journal of Physicochemical and Engineering Aspects, 2017;124:427-445.
20. 20.Zhiqiangzhu. Determination of gel time and gel point of epoxy-amine thermo sets by in-situ near infrared spectroscopy Polymer Testing. International Journal of Pharmaceutical Dosage forms, 2018; 72:416-422.