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Research Article

PREPARATION, CHARACTERIZATION AND IN-VITRO EVALUATION OF SUSTAINED RELEASE MICROSPHERES CONTAINING PROPAFENONE

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ABSTRACT

Propafenone Is A Class IC Anti Arrhythmic Agent. It Shows Good Bioavailability, averaging up to 98% up on oral administration. An absorption maximum was found to be 247nm.Diseased state influences the gastric emptying rate. Incomplete absorption of the drug is often accompanied by lesser Bioavailability. After Oral Administration Of Propafenone HCL would be stay in the stomach and issue the drug in a sustained manner, so that the drug could be released un sealing to its sight of absorption in the upper GIT, this method of administration would be finest achieving the effect of the drug. Based on this, an effort was made to design controlled release microspheres of Propafenone hydrochloride using different proportions of polymers and combinations.

In the Present effort Controlled Release Micro Spheres Of Propafenone HCL by Selecting Sodium Alginate and Methocele50 as Polymers. The polymers are used in different ratios. All the formulations were prepared by Solvent Evaporation Method. The preparation of all the formulations showed decent flow properties such as angle of repose, bulk density, tapped density. The Prepared Microspheres showed Good Post Formulation Parameters such as Content Uniformity, % Yield; Dissolution Studies, Stability Studies and they passed all the Quality Control Evaluation Parameters as Per I.P Limits. Among the entire Formulations T2 Formulation showed Maximum % Drug Release, but the Ideal Formulation was found to be T7 for showing best Drug Release i.e., 100% in 10 Hours. Hence It Is Considered As Optimized Formulation with the least possible concentrations of Polymers. It was observed that the Combination ratio Of Sodium Alginate 400mg and Methocel E50 40mg has distinct effect on Invitro Drug Release profiles when compared to all the other combinations of polymers.

Keywords: Propafenone Hydrochloride, Sodium Alginate, Controlled Released Microspheres.

INTRODUCTION

Microspheres play a completely vital function as particulate drug shipping system because of their small length and different inexperienced property. Microspheres proved to be an appropriate bridge to formulate a powerful dosage form, to simulate controlled drug release. Microspheres are in general loose flowing stable powders, which encompass proteins or artificial polymer that are bio degradable in nature. Microspheres of particle size between 0.1-200 µm can be deliver by numerous route like oral, parental, nasal, ophthalmic, transversal, colonel etc. In future by combining new strategy, microspheres will come across a central position in novel drug delivery, mainly in unhealthy cell taxonomy, genetic material, targeted and efficient drug delivery. [1]

Micro particle of spherical shape without membrane or any distinct outer layer. The nonappearance of outer layer form a distinctive phase which is important to differentiate micro sphere from micro capsule because it leads to first-order diffusion phenomena, while diffusion is zero order in the case of microcapsule. A properly designed managed drug delivery gadget can overcome some of the problems of conventional therapy and beautify the therapeutic efficacy of a drug. There is a selection of methods in turning in a therapeutic substance to the goal website online in a sustained managed release fashion. It is the reliable approach to supply the drug to the target web site with specificity, if changed, and

to preserve the desired awareness at the website of hobby without sick-timed outcomes. Microspheres obtained a whole lot interest now not handiest for extended release, however also for concentrated on of anticancer tablets to the tumors In future via combining one of a kind other strategies, microspheres will locate the important location in novel drug delivery, specifically in diseased cell sorting, diagnostics, genetic cloth, secure, focused and green in vivo delivery and organ and tissues inside the corpse.[2]

As microspheres are hollow from inner and drug is loaded at outer shell with polymer, the drug is slowly released from the outer shell while they arrive into contact with gastric fluid. Due to low density than the gastric fluid they showed extremely good buoyancy for greater than 12 hrs and launched the drug for that lots time frame.

Polystyrene microspheres are usually used in biomedical packages because of their capacity to facilitate methods together with cellular sorting and immune precipitation. Proteins and ligand adsorb onto polystyrene without problems and enduringly, which make polystyrene microspheres appropriate for medical studies and organic laboratory experiments. Four Polyethylene microspheres are typically used as strong or transient filler. Lower melting temperature permits polyethylene microspheres to create porous structures in ceramics and different fabric. Lofty sphericity of poly ethylene microspheres, in addition to accessibility of dyed and fluorescent microspheres, makes them enormously proper for flow visualization and fluid drift analysis, microscopy technique, health sciences and several research applications.[3]

Charged polyethylene microspheres are also utilized in electronic paper virtual displays. Expandable micro spheres are polymer microspheres which are used as a blowing agent in e.g. blow ink, automobile below carcass coating and shot molding of thermoplastics. They also can be used as mild weight filler in e.g. cultured marble, waterborne paints and crack fillers/joint compound. Expandable polymer microspheres can expand to extra than 50 instances their unique length while warmness is carried out to them. The exterior wall of every sphere is a thermoplastic shell that encapsulates a low boiling point hydrocarbon. whilst heated, this outside shell melt and amplify as the hydrocarbon exert a stress at the inner shell wall[4]

Glass microspheres are on the whole used as a filler and volumizer for weight reduction, reflector (Cataphote) for dual carriageway safety, a preservative for cosmetics. Microspheres made from rather transparent glass can perform as very high excellent optical micro-cavities or optical micro resonators. Ceramic microspheres are used more often than not as grinding media.

Substances used in Microsphere preparation typically are polymers. They may be classified into types:[5]

1. Artificial Polymers
2. Natural polymers

1. Synthetic polymers are divided into two sorts

a. Non-biodegradable polymers e.g. Poly methyl meth acryl past due (PMMA) three Acrolein4 Glycidyl methacrylate Epoxy polymers b. Biodegradable polymers e.g. Lactates, Glycol ideas & their co polymers5 Poly alkyl Ciano acrylates Poly anhydrides.

2. **Herbal polymers**

acquired from distinct resources like proteins, carbohydrates, and chemically modified carbohydrates.

a. **Proteins**

Albumin, Gelatin, and Collagen.

b. **Carbohydrates**

Agarose, Carrageenan, Chitosan, Starch

c. Chemically changed carbohydrates: poly dextran, Polystarch. In case of non-bio degradable drug carriers, whilst administered determine rally, the service ultimate within the body after the drug is absolutely launched poses opportunity of service toxicity over an extended time period. Bio degradable companies which degrade in the body to non-toxic degradation merchandise do not pose the problem of carrier toxicity and are more appropriate for parenteral programs.

1. Artificial polymers[6, 7, 8]

Poly alkyl cyano acrylates is a capability drug service for parenteral as well as different ophthalmic, mouth arrangements; anti-tumor dealers inclusive of cisplatin, cyclo phosphate amide, and Doxa Rubicon.

Sustained launch arrangements for anti malarial drug in addition to for lots other pills were formulated by means of using of copolymer of poly lactic acid and poly glycolic acid

Poly anhydride microspheres (40µm) have been investigated to extend the precorneal residence time for ocular delivery

Poly adipic anhydride is used to encapsulate timolol male ate for ocular delivery. Poly acrolein microspheres are functional type of microspheres. They do not require any activation step since the surfacial free CHO

groups over the poly acrolein can react with NH2 group of protein to form Schiff's base.

2. Herbal polymers

Albumin is a extensively distributed natural protein. it's far considered as a ability provider of drug or proteins (for either their web site precise localization or their local utility into anatomical discrete sites). it is being broadly used for the targeted drug for the centered drug delivery to the tumor cells. Gelatin microspheres can be used as green provider device capable of handing over the drug or organic response modifiers including interferon to phagocyte. Starches eight belong to carbohydrate institution. It includes precept glucopyranose unit, which on hydrolysis yields D-glucose. Its miles a polysaccharide include a massive number of loose OH agencies. Via which a huge number of energetic elements can be integrated within as well as on the floor of microspheres.

Chitosan is a deacylated from chitin. The upshot of chitosan has been taken into consideration due to its accusation. It's far unfathomable at impartial and alkaline Ph value however bureaucracy a salt with inert and rudimentary salt. Upon dissolution, the amino groups of chitosan get protonated, and the ensuing polymer turns into definitely charged.[9]

Techniques of practice[10, 11]

The guidance of microsphere ought to persuade company standards:

1. The capacity to comprise reasonably excessive concentrations of the drug.
2. Balance of the training after synthesis with a clinically appropriate shelf life.
3. Controlled particle length and dispersability in aqueous motors for injection.
4. Release of energetic reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability.

1. Single emulsion method

The micro particulate vendors of herbal polymer i.e. those of protein and carbohydrate can be organized with the aid of single emulsion approach. The natural polymers are dissolving or disperse in aqueous medium followed by using dispersion in non-aqueous medium like oil. The move linking can be reaping each by means of way of warmth and by the use of the chemical move linkers. The chemical cross linking agents used are glutaraldehyde, form aldehyde; di acid chloride and so forth. High temperature denaturation is not suitable for thermo labile substances.

2. Double emulsion technique[12]

Double emulsion approach of microspheres training includes the formation of the a couple of emulsions or the double emulsion of kind w/o/w and is fine acceptable to water soluble drugs, peptides, proteins and the vaccines. This approach can be used with each the natural as well as synthetic polymers. The aqueous protein answer is dispersed in a lipophilic natural non-stop section. The continuous phase is normally consisted of the polymer solution that ultimately encapsulates of the protein contained in dispersed aqueous segment. The number one emulsion is subjected then to the homogenization or the sonicator earlier than addition to the aqueous solution of the poly vinyl alcohol (PVA). These consequences results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either through solvent evaporation or via solvent extraction. some of hydrophilic capsules like luteinizing hormone freeing hormone (LH-RH) agonist, vaccines, proteins/peptides and so on., are efficiently integrated into the microspheres the use of the technique of double emulsion. The polymer erosion, i.e. loss of polymer is followed via accumulation of the monomer within the release medium. The carrying away of the polymer begins with the changes in the microstructure of the service as water penetrates within it leading to the plasticization of the matrix. The geometry of the provider, i.e. whether it is reservoir kind wherein the drug is gift as core or matrix type wherein drug is dispersed during the provider, governs average release profile of the drug or lively ingredients.

3. Polymerization strategies[13]

The polymerization techniques conventionally used for the practice of the microspheres are particularly categorized as:

I. regular polymerization

II. Interfacial polymerization. Each is performed in liquid segment.

Regular polymerization

Its miles carried out the usage of exceptional techniques as bulk, suspension, precipitation, and emulsion and micelles polymerization technique. In mass, a monomer or a concoction of monomers in conjunction with the initiator or catalyst is commonly heated to provoke polymerization. Polymer so acquired may be molded as microsphere. Drug load may be executed at some point of the manner of polymerization.

Suspension polymerization
additionally referred as a bead or pearl polymerization. Here it's miles finished by heating the monomer or combination of monomers as droplets dispersion in a non-stop aqueous segment. The droplets may additionally contain an initiator and different additives. Emulsion polymerization range as of suspension polymerization because of the presence initiator inside the aqueous section, which afterward diffuses to the floor of micelles.

Interfacial polymerization
It includes the response of diverse monomers at the interface among the 2 immiscible liquid levels to form a movie of polymer that basically envelops the dispersed section.

Segment separation coacervation technique[14]
This technique is based at the precept of lowering the solubility of the polymer in the organic phase to affect the formation of polymer rich section referred to as the coacervates, on this technique, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is brought to the machine. Addition of non-solvent results in the solidification of the polymer. Poly lactic acid (PLA) microspheres were prepared by this approach by using the usage of butadiene as an incompatible polymer. Consequently the system variables are vital as they control the kinetic of the fashioned debris seeing that there is no described nation of equilibrium attainment.

5. Spray drying and spray congealing [15, 16]
Those strategies are based on the drying of the mist of the polymer and drug within the air. Depending upon the removal of the solvent or cooling of the solution, the 2 tactics are named spray drying and spray congealing respectively. The polymer is first dissolved in the suitable unstable natural solvent together with dichloromethane, acetone, etc. This dispersion is then atomized in a stream of warm air. The spray drying manner is used to encapsulate a variety of penicillin. Very fast solvent evaporation, however, ends in the formation of porous micro particles.

DISTINCT FORMS OF MICROSPHERES
1. Bio adhesive micro spheres[17, 18]
Adhesion of drug transport device to the mucosal membrane inclusive of buccal, ocular, rectal, nasal and many others. Can be termed as bio adhesion. the ones styles of microspheres exhibit a prolonged residence time on the site of utility and reason intimate contact with the absorption website online and produce better therapeutic motion.

2. Magnetic microspheres [19]
This sort of transport machine may be very tons crucial which localizes the drug to the sickness web page. Magnetic providers acquire magnetic responses to a magnetic discipline from integrated materials which can be used for magnetic microspheres are chitosan, dextran and many others. The exceptional forms of Magnetic micro spheres are
A. therapeutic magnetic microspheres used to deliver the chemotherapeutic agent to liver tumors.
B. Diagnostic microspheres, used for imaging liver metastases.

3. Floating microspheres[20]
In floating sorts, the majority density is much less than the gastric fluid and so remains buoyant inside the stomach without affecting the gastric emptying fee. The drug is launched slowly on the favored rate, and the gadget is determined to be floating on gastric content material and increases gastric house and will increase fluctuation in plasma concentration. Drug (propafenone) is given in the shape of floating microspheres.

4**. Radioactive microspheres**
Radio embolism therapy microspheres sized 10-30 nm are of large than the diameter of the capillaries and gets tapped in first capillary bed once they stumble upon. It differs from drug transport machine, as radio activity is not launched from microspheres but acts from inside a radioisotope common distance and the distinctive kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

5. Polymeric microspheres[21]
The unique varieties of polymeric microspheres can be categorized as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.
Biodegradable polymeric microspheres
Herbal polymers including starch are used with the idea that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable polymers prolongs the house time when touch with mucous membrane due to its high diploma of swelling belongings with aqueous medium , consequences gel formation. The charge and volume of drug launch is managed by means of attention of polymer and the release pattern sustained manner.

Synthetic polymeric microspheres[22]

Artificial polymeric microspheres are widely used in medical software, furthermore that extensively utilized as bulking agent, fillers, embolic particles, drug transport vehicles and so forth. and proved to be safe and biocompatible however the predominant disadvantage of those type of microspheres, are have a tendency to migrate faraway from injection web page and cause potential chance, embolism and further organ harm.

VARIABLES INFLUENCING DRUG RELEASE FROM MICROSPHERES [23]

There are following elements which without delay/in a roundabout way affect the drug launch characteristics of the microspheres

A. Concentration of the polymer in dispersed phase: because the polymer awareness in aqueous phase will increase, size of microspheres is improved this outcomes increase in time and slower drug launch from microspheres.

B. Drug: Polymer Ratio (DPR)

Drug launch from microspheres is tormented by the ratio of the drug to the polymer as growing in the first causes quicker drug release. By growing the quantity of drug loading, a point might be reached when the solid drug debris upon dissolution will start to form non-stop pores or channels in the matrix. In different words, as the amount of drug content material is multiplied the matrix becomes extra porous as drug is leached out from the polymer and accordingly faster drug release price occurs. Consequently, the drug release from micro pellets organized at lower drug- polymer ratios changed into quicker than that of micro pellets prepared at higher drug- polymer ratios due to the small size of the micro pellets, which furnished a huge surface area for quicker drug release

C. Selection of solvent machine for the dispersed phase: selection of solvent gadget based at the volatility of solvent, solubility of polymer and type of technique of education used for training of microspheres. Solvent should have excessive volatility and high polymer solubility.

D. Effect of Temperature

Microspheres organized at 60°C showed quicker drug launch than the microspheres prepared at 10°C. This could be attributed to the lower in viscosity of the oily segment as the temperature will increase, which in flip decrease the microspheres

E. Effect of stirring speed

The drug release charge changed into growing on increasing the stirring fee. Drug launch changed into higher inside the case of microspheres prepared at a better stirring charge but at low stirring fee the release price was slow. This can be attributing that smaller length microspheres have a larger floor region uncovered to dissolution medium, giving upward thrust to faster drug release.

Applications [24]

New applications for microspheres are discovered every day, below are just a few

1. Assay - Coated microspheres provide measuring tool in biology and drug research
2. Buoyancy - Hollow microspheres are used to decrease material density in plastics (glass and polymer)
3. Particle image velocimetry - Solid microspheres used for flow visualization, typically with density matching that of the fluid.
4. Ceramics - Used to create porous ceramics used for filters (microspheres melt out during firing, Polyethylene Microspheres) or used to prepare highstrength lightweight concrete.
5. Cosmetics - Opaque microspheres used to hide wrinkles and give color, Clear microspheres provide "smooth ball bearing" texture during application (Polyethylene Microspheres)
6. De convolution - Small fluorescent microspheres (less than 200 nanometers) are required to obtain an experimental Point spread function to characterize microscopes and perform image de convolution
7. Drug delivery - As miniature time release drug capsule made of, for example, polymers. A similar use is as outer shells of micro bubble contrast agents used in contrast-enhanced ultrasound.
8. Electronic paper - Dual Functional microspheres used in Garcon electronic paper
9. Insulation – expandable polymer microspheres are used for thermal insulation and sound dampening.
10. Personal Care - Added to Scrubs as an exfoliating agent (Polyethylene Microspheres)
11. Spacers Used in LCD screens to provide a precision spacing between glass panels (glass)
12. Standards – mono disperse microspheres are used to calibrate particle sieves, and

particle counting apparatus.

13. Retro reflective - added on top of paint used on roads and signs to increase night visibility of road stripes and signs (glass)
14. Thickening Agent - Added to paints and epoxies to modify viscosity and buoyancy
15. Drugs can be formulated as HBS floating microsphere.

MATERIAL AND METHODS

API Propafenone was collected form sreepathi pharmaceuticals private limited and excipients sodium alginate, Methocel E-50, calcium chloride, sodium lauryal sulphate are procures from SD Fine chemicals-Hyderabad.

METHODOLOGY

ANALYTICAL METHODS DEVELOPMENT OF PROPAFENONE[25]

U.V Visible Spectroscopy

Scanning of Propafenone in 0.1N HCl

The solution containing 100µg/ml of Propafenone in 0.1 N HCl become prepared and scanned over the wavelength of 2 hundred-four hundred nm towards 0.1 N HCl as blank by means of double beam UV spectrophotometer. The plot of absorbance vs. wavelength can be recorded using double beam UV spectrometer.

Preparation of standard stock solution

Standard plot of Propafenone in 0.1 N HCl (linearity)

0.1N HCl was prepared by using 9.5ml of accurately weighed HCl which was taken in to a 1000ml volumetric flask. To the stock solution 10mg of the drug was added for preparing the standard plot.

Preparation and dilutions of standard solution for the construction of calibration curve of Propafenone

From the stock solution, further dilutions were made with 0.1N HCL in 10ml volumetric flasks to get the solutions in the range of 10-50µg/ml.

From the working standard solution 2ml was diluted to 10ml with 0.1NHcl to give 10 µg/ml concentrated solutions. From dilution 1, take 2ml, 4ml, 6ml, and 8ml and so on... Of solution, was diluted up to mark in 10ml volumetric flask to obtain 10, 20, 30, 40 and 50 µg/ml concentrated solutions. The absorbance's of these concentrations was noted was noted at λ_{max}=247.00nm wave length and record next to a suitable blank using U.V Spectro photo meter (UV -1601, Shimadzu, PG Instruments ltd, Japan) A Calibration curve of Absorbance vs. concentration is plotted and the drug follows Beer Lamberts Law in the concentration assortment of 10-50µg/ml. the following absorbance's were noted from the UV spectra

Table 1: Absorbance against each concentration

Concentration	Absorbance(nm)
10µg/ml	0.373
20 µg/ml	0.505
30 µg/ml	0.608
40 µg/ml	0.653
50 µg/ml	0.853

Y=0.011x+0.266 ; R2= 0.965.

Compatibility Studies

Drug-Excipients interaction study (FTIR Spectroscopy)

The compatibility of the drug and polymer under experimental conditions is an important criterion before formulation. It is necessary to confirm that the drug does not react with the polymer effect the shelf life of the product. This can be confirmed by carrying out infrared spectroscopy analysis by using Fourier Transformation infrared spectrophotometer Alpha Brooke FTIR (Tokyo, Japan).The instrument was calibrated using polystyrene film.

Procedure

The obtained drug and polymer were subjected to FTIR studies. In the present cram potassium bromide disc pellets method was in work and the achieve FTIR spectra's were analyzed comparatively, with reference spectrum of Propafenone.

Table 2: Formulation of Propafenone sustained release Microspheres

Ingredients	F1	F2	F3	F4	F5	F6	F7
Propafenone	100	100	100	100	100	100	100
Na. Alginate	100	140	300	380	460	380	400
Methocel E50	-	-	-	-	10	20	40
CaCl2	50	50	50	50	50	50	50
Water	20	20	20	20	20	20	20
(SLS)	5	5	5	5	5	5	5
Titanium dioxide	5	5	5	5	5	5	5

Method followed is phase separation emulsion technique

1. Initially prepare a polymer solution i.e.,40mg sodium alginate in 20ml water taken in a 50ml beaker.
2. To this slowly add 20mg of drug (propafenone).
3. Allow it for stirring, under a mechanical stirrer for at least 10 – 15min.
4. Due to excessive stirring, bubbles will be formed in the solution which can be removed by addition of 5mg S.L.S. under a digital ultra sonicator.
5. Then in another beaker take 5%Cacl2 (i.e.; 5gm in 100ml H2O) and mix it properly to figure a consistent solution.
6. Then with the aid of a needle, add the prepared polymer solution drop wise into the Cacl2 solution.
7. Transparent micro beads can be observed in the cacl2 solution, these micro beads are nothing but the microspheres.
8. Filter the solution to separate the microspheres.
9. The separated microspheres are kept a side till 15-20 min for drying in a tray drier at 60 degrees until all the moisture is evaporated.
10. Add Titanium dioxide to the above formulated microspheres to make them stable for a longer duration.
11. These microspheres are then evaluated and characterized for their quality and in-vitro dissolution studies.

EVALUATION PARAMETERS OF PROPAFENONE

Bulk density

It is the ratio of the overall mass of powder to the majority quantity of powder. It's far measured by way of pouring the weighed powder in measuring cylinder and initial weight was stated. This preliminary volume is called as the majority quantity.

It far expressed in g/ml and is given via method

$$Db = M/Vb$$

In which M =mass of powder

Vb = bulk extent of powder.

Tapped density

After carrying out the procedure as given in the dimension of bulk density, the cylinder containing the sample is tapped the use of an appropriate mechanical tapped density tester that provides one hundred drops in keeping with minute and this became repeated till distinction among succeeding size is much less than 2% after which tap volume changed into measured to the nearest graduated unit.

The tapped density is expressed in g/ml and is calculated the usage of system

$$D\_ (t) = M/Vt$$

Wherein M – mass of powder

Vt- tapped quantity of powder.

The angle of repose

It's far the maximum perspective viable among the floor of the pile of powder and the horizontal aircraft. The microspheres have been allowed to float thru the funnel constant to a stand at specific peak. The attitude of repose becomes then calculated by using measuring the height and radius of the heap of microspheres shaped. Care turned into taken to see that the microspheres align and roll over each different via the edges of the funnel.

It is given through - **Tan= h/r**

$$\theta = [\tan]^{(-1)} h/r.$$

Where ɵ =angle of repose;

h=height in cm and r = radius in cm

Compressibility Index

It indicates powder flow properties. It is expressed in % and is given by

$$\frac{D_t - D_b}{D_t} * 100$$

Content uniformity

Microspheres with pre-determined weight from each batch were taken and weight equivalent to10mg & transfer to a 250 ml volumetric hip flask with 0.1N HCl. The quantity was then set up to the blotch with 0.1N HCl. The solution was filtered and the filtrate was sufficiently diluted and the absorbance was recorded against the blank at 247 nm. The drug content of the Standard containing the drug powder was also determined.

In-Vitro Drug Release Studies

The release rate of (Propafenone) drug from the polymeric microspheres was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C with 50 rpm. An appetizer (5 ml) of the solution is introverted from the dissolution apparatus hourly for 8 hours, and the samples were replaced with fresh dissolution medium. The sample is diluted to an appropriate

concentration by 0.1N HCl. Absorbance of the following solutions is calculated at 254 nm by means of a UV-Visible spectrophotometer. Increasing percentage of drug release was considered using the equation obtained from a standard curve.

RESULTS AND DISCUSSIONS

U.V-visible spectrophotometer

Prepared different concentrations of solution of Propafenone was allowed to run in UV spectroscopy for finding of linearity of absorbance, different absorbance against different concentrations are given below table and graphical representation was given in figure no….. with R^2 value 0.992.

Table 3: Concentration vs. absorbance

S.No	Con in µg/ml	Absorbance nm
1	10	0.373 nm
2	20	0.505 nm
3	30	0.608 nm
4	40	0.653 nm
5	50	0.853 nm

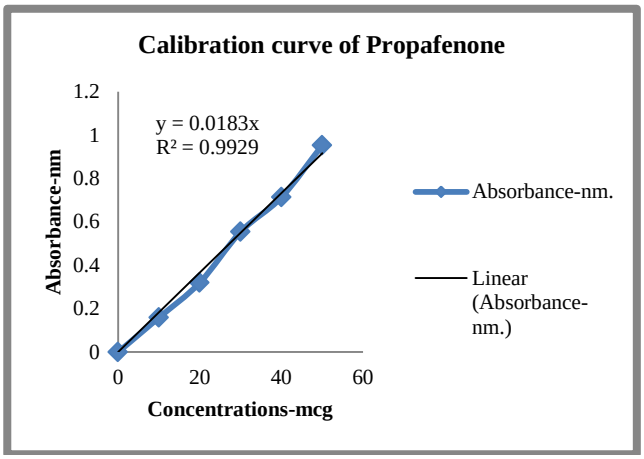
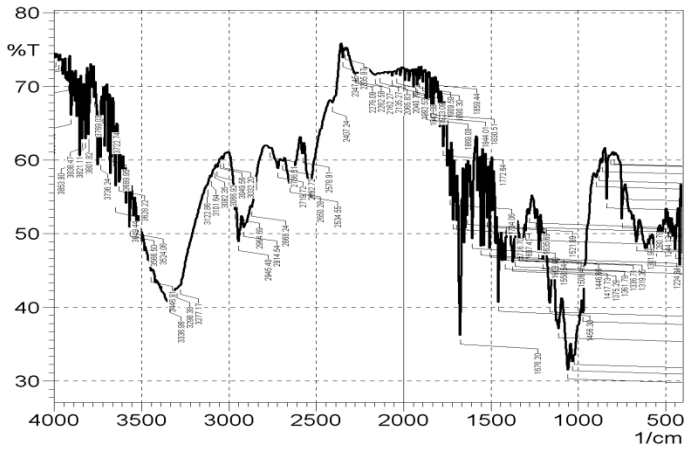


Fig. 1: calibration curve of Propafenone

FTIR STUDIES

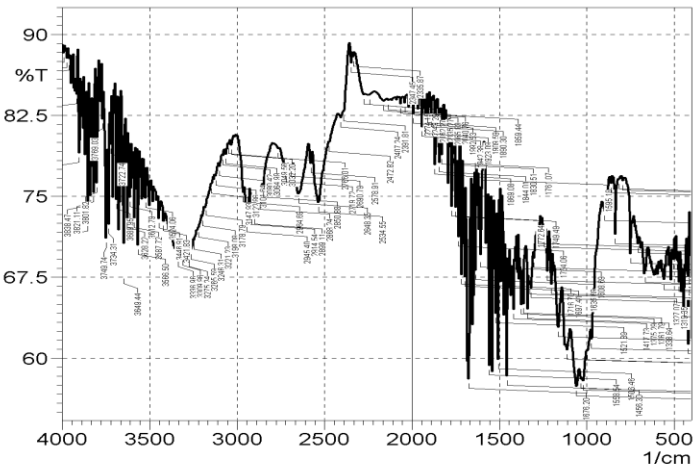
Compatibility Studies

Propafenone and other excipients used in the preparation of Microspheres were found to be compatibility between them, based on the FTIR spectra obtained. The details of FTIR spectra of pure PROPAFENONE and polymers are be determined from following FTIR spectra.



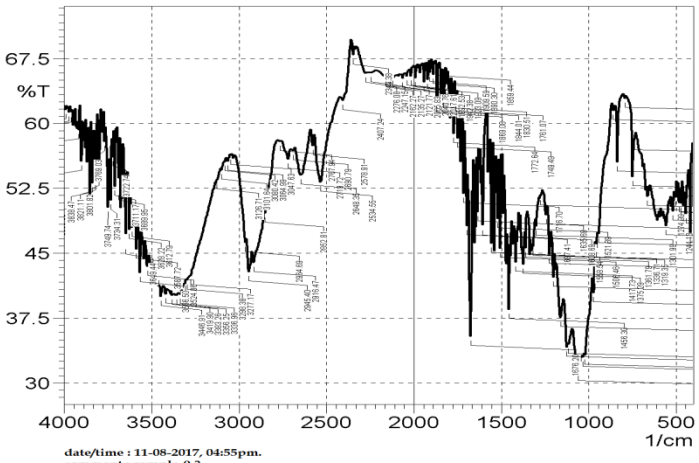
	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	418.57	45.781	9.632	428.21	412.78	4.452	0.47
2	435.93	50.995	0.786	437.86	430.14	2.172	0.017
3	443.64	47.899	3.001	453.29	439.78	4.139	0.172
4	472.58	50.218	1.585	474.5	464.86	2.791	0.051
5	482.22	50.859	1.482	486.08	476.43	2.781	0.066
6	503.44	51.324	1.323	509.22	497.65	3.284	0.071
7	518.87	49.055	1.441	520.8	511.15	2.867	0.062
8	559.38	46.858	3.473	572.88	540.09	10.206	0.463
9	665.46	48.922	0.779	667.39	650.03	5.137	0.045
10	738.76	55.926	0.428	742.62	732.97	2.406	0.015
11	748.41	52.058	5.137	761.91	742.62	4.861	0.269
12	794.7	60.694	0.359	800.49	788.91	2.495	0.014
13	815.92	60.613	0.199	821.7	802.41	4.168	0.016
14	837.13	54.757	6.505	846.78	823.63	5.317	0.369
15	862.21	59.682	0.842	866.07	848.71	3.75	0.029
16	881.5	58.441	0.535	885.36	868	3.916	0.016
17	896.93	57.66	0.793	910.43	885.36	5.925	0.077
18	972.16	39.305	2.56	976.01	912.36	18.979	0.161
19	1022.31	33.469	0.386	1024.24	977.94	19.821	0.055
20	1033.88	32.632	1.563	1043.52	1026.16	8.264	0.171
21	1058.96	31.52	5.254	1091.75	1045.45	21.029	1.478
22	1112.96	37.104	2.032	1120.68	1093.67	11.063	0.28
23	1163.11	40.585	6.87	1184.33	1143.83	14.478	1.36
24	1203.62	46.448	4.74	1215.19	1195.91	5.942	0.35
25	1224.84	47.828	4.896	1236.41	1217.12	5.693	0.337
26	1244.13	52.074	1.719	1263.42	1238.34	6.805	0.139
27	1280.78	52.7	1.19	1286.56	1265.35	5.711	0.1
28	1301.99	50.424	0.833	1303.92	1288.49	4.352	0.035
29	1319.35	47.623	0.761	1321.28	1305.85	4.719	0.048
30	1336.71	47.526	1.311	1346.36	1334.78	3.632	0.118
31	1361.79	46.759	3.127	1365.65	1348.29	5.23	0.115
32	1375.29	46.146	2.593	1383.01	1367.58	4.974	0.161
33	1417.73	46.448	2.882	1421.58	1408.08	4.207	0.134
34	1446.66	46.877	1.061	1448.59	1442.8	1.791	0.003
35	1456.3	40.697	7.31	1462.09	1452.45	3.416	0.34
36	1506.46	48.027	11.888	1512.24	1502.6	2.572	0.426
37	1521.89	52.156	7.874	1529.6	1514.17	3.887	0.454
38	1558.54	48.355	12.169	1562.39	1548.89	3.304	0.387
39	1608.69	49.213	8.482	1612.54	1583.61	6.896	0.535
40	1635.69	52.463	7.513	1641.48	1631.83	2.376	0.235
41	1676.2	36.211	19.682	1691.63	1666.55	8.697	2.406

Fig. 2: FTIR Spectrum of Pure Propafenone



	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	418.57	61.295	10.932	428.21	412.78	2.602	0.411
2	435.93	68.071	1.324	437.86	430.14	1.205	0.031
3	443.64	64.742	3.421	449.43	439.78	1.724	0.119
4	472.58	67.09	2.763	476.43	464.86	1.884	0.081
5	482.22	69.09	1.359	488.01	478.36	1.52	0.052
6	503.44	69.125	1.532	511.15	497.65	2.106	0.069
7	549.73	68.5	0.424	551.66	542.02	1.551	0.023
8	559.38	67.219	1.002	563.23	551.66	1.956	0.046
9	665.46	67.931	0.858	667.39	650.03	2.771	0.038
10	705.97	70.682	0.655	711.76	702.11	1.437	0.023
11	748.41	69.704	3.665	781.2	742.62	4.95	0.14
12	794.7	76.464	0.36	800.49	788.91	1.338	0.012
13	815.92	76.603	0.045	817.85	802.41	1.772	0.001
14	837.13	71.521	5.192	846.78	819.77	3.362	0.249
15	862.21	76.205	0.648	866.07	856.42	1.122	0.019
16	896.93	73.629	1.587	910.43	868	5.32	0.19
17	972.16	61.787	1.626	976.01	912.36	10.11	0.073
18	997.23	60.699	0.22	999.16	977.94	4.479	0.048
19	1020.38	57.911	0.866	1026.16	1001.09	5.718	0.076
20	1031.95	57.107	0.302	1041.6	1028.09	3.161	0.02
21	1058.96	57.413	2.745	1093.67	1043.52	11.368	0.522
22	1112.96	60.79	0.947	1120.68	1095.6	5.284	0.088
23	1163.11	62.878	4.651	1184.33	1143.83	7.57	0.662
24	1201.69	66.883	3.391	1215.19	1195.91	3.107	0.19
25	1224.84	68.081	3.721	1236.41	1217.12	2.959	0.186
26	1244.13	71.167	1.233	1255.7	1238.34	2.488	0.063
27	1280.78	71.503	0.523	1284.63	1265.35	2.731	0.036
28	1301.99	69.288	0.677	1303.92	1292.35	1.772	0.028
29	1319.35	66.496	1.012	1321.28	1305.85	2.567	0.048
30	1327.07	66.827	0.639	1332.86	1323.21	1.676	0.028
31	1338.64	64.563	3.969	1346.36	1334.78	1.997	0.117
32	1361.79	65.044	3.71	1365.65	1352.14	2.253	0.107
33	1375.29	64.968	3.595	1383.01	1367.58	2.696	0.157
34	1417.73	64.527	4.567	1425.44	1408.08	2.939	0.177
35	1456.3	58.354	9.441	1462.09	1452.45	1.946	0.318
36	1506.46	59.895	14.766	1512.24	1502.6	1.644	0.42
37	1521.89	64.189	9.766	1529.6	1514.17	2.491	0.462
38	1558.54	59.357	15.152	1562.39	1552.75	1.615	0.376
39	1595.18	77.405	0.751	1597.11	1587.47	1	0.015
40	1608.69	69.352	7.001	1612.54	1599.04	1.855	0.307
41	1635.69	68.161	9.804	1641.48	1631.83	1.277	0.235

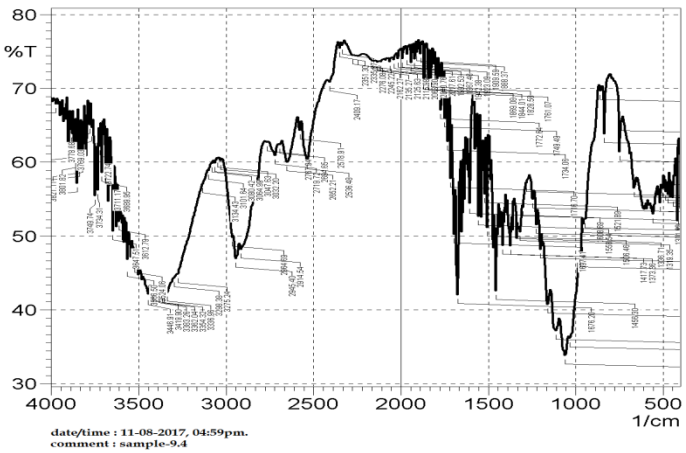
Fig. 3: FTIR Spectrum of Sodium Alginate



SHIMADZU

	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	418.57	47.367	8.419	428.21	412.78	4.308	0.382
2	435.93	52.699	0.853	439.78	430.14	2.619	0.023
3	443.64	49.565	3.041	449.43	439.78	2.823	0.132
4	472.58	50.798	1.496	474.5	464.86	2.717	0.043
5	482.22	50.842	1.953	488.01	476.43	3.32	0.104
6	503.44	51.489	1.215	509.22	497.65	3.278	0.068
7	518.87	49.906	1.272	520.8	511.15	2.821	0.055
8	557.45	48.178	1.348	563.23	532.37	9.308	0.119
9	663.53	51.586	0.915	667.39	650.03	4.901	0.064
10	738.76	58.036	0.466	742.62	732.97	2.251	0.016
11	748.41	53.855	4.997	786.98	742.62	9.673	0.24
12	792.77	62.918	0.367	800.49	788.91	2.314	0.016
13	837.13	55.544	6.657	844.85	802.41	8.972	0.384
14	860.28	61.508	0.677	866.07	856.42	2.015	0.026
15	943.22	47.274	0.821	947.08	868	20.41	0.091
16	956.72	45.652	1.003	960.58	949.01	3.848	0.045
17	972.16	40.454	3.249	977.94	962.51	5.69	0.255
18	1022.31	33.237	0.514	1024.24	979.87	18.977	0.15
19	1033.88	32.998	0.299	1039.67	1026.16	6.469	0.026
20	1058.96	31.353	2.885	1093.67	1041.6	25.064	1.101
21	1116.82	34.483	0.212	1118.75	1095.6	10.461	0.049
22	1126.47	34.167	1.712	1143.83	1120.68	10.154	0.142
23	1161.19	37.571	3.738	1184.33	1145.75	15.588	0.881
24	1201.69	42.251	3.47	1215.19	1195.91	6.771	0.282
25	1224.84	44.929	3.75	1236.41	1217.12	6.272	0.262
26	1244.13	49.45	1.464	1263.42	1238.34	7.383	0.122
27	1274.99	51.655	0.143	1276.92	1265.35	3.291	0.009
28	1301.99	48.162	0.751	1303.92	1284.63	5.79	0.034
29	1319.35	45.829	0.588	1321.28	1305.85	5.001	0.035
30	1336.71	45.93	1.073	1350.22	1334.78	4.999	0.096
31	1361.79	45.617	2.553	1365.65	1352.14	4.282	0.09
32	1375.29	43.727	2.557	1383.01	1367.58	5.321	0.169
33	1417.73	43.974	3.847	1425.44	1408.08	5.823	0.261
34	1456.3	38.508	8.196	1462.09	1442.8	6.911	0.631
35	1506.46	45.588	10.976	1512.24	1502.6	2.796	0.409
36	1521.89	49.014	6.986	1529.6	1514.17	4.32	0.43
37	1558.54	46.182	11.489	1562.39	1552.75	2.681	0.368
38	1608.69	48.136	7.861	1612.54	1585.54	6.765	0.499
39	1635.69	49.788	6.99	1641.48	1631.83	2.602	0.231
40	1676.2	35.414	17.516	1691.63	1666.55	9.095	2.196
41	1697.41	48.216	6.375	1708.99	1693.56	4.404	0.458

Fig. 4: FTIR Spectrum of Methocel E-15



SHIMADZU

	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	418.57	52.088	10.014	428.21	410.85	3.996	0.403
2	435.93	58.116	0.987	439.78	430.14	2.207	0.031
3	443.64	55.227	2.714	449.43	439.78	2.398	0.112
4	472.58	55.67	1.694	474.5	464.86	2.337	0.055
5	484.15	56.033	1.514	488.01	476.43	2.861	0.076
6	503.44	56.434	1.166	509.22	497.65	2.822	0.059
7	516.94	54.492	1.809	520.8	511.15	2.45	0.06
8	559.38	52.974	1.198	563.23	532.37	8.06	0.139
9	665.46	56.509	1.199	669.32	653.89	3.751	0.078
10	738.76	65.479	0.378	742.62	732.97	1.753	0.011
11	748.41	61.41	5.153	775.41	742.62	5.598	0.225
12	837.13	63.836	6.68	844.85	802.41	6.624	0.351
13	862.21	69.654	0.749	866.07	856.42	1.495	0.023
14	947.08	52.284	0.922	950.94	868	17.726	0.225
15	956.72	51.675	0.703	960.58	950.94	2.737	0.028
16	972.16	47.035	2.185	976.01	962.51	4.15	0.138
17	1033.88	36.175	1.351	1039.67	977.94	24.262	1.002
18	1060.88	33.664	1.355	1070.53	1041.6	13.241	0.257
19	1114.89	37.194	0.591	1120.68	1095.6	10.607	0.123
20	1161.19	40.746	4.511	1184.33	1145.75	14.082	0.935
21	1201.69	48.212	2.971	1217.12	1195.91	6.31	0.238
22	1224.84	51.556	2.86	1236.41	1219.05	4.718	0.166
23	1246.06	54.978	1.817	1263.42	1238.34	6.251	0.153
24	1282.71	57.235	0.129	1284.63	1265.35	4.598	0.01
25	1301.99	53.922	0.516	1303.92	1284.63	4.876	0.018
26	1319.35	50.594	0.872	1321.28	1305.85	4.347	0.068
27	1336.71	50.874	1.267	1350.22	1334.78	4.324	0.096
28	1373.36	48.707	2.741	1381.08	1367.58	4.043	0.145
29	1417.73	48.719	4.65	1425.44	1408.08	5.002	0.273
30	1456.3	42.602	7.853	1460.16	1440.87	5.892	0.433
31	1506.46	51.17	12.638	1512.24	1502.6	2.282	0.4
32	1521.89	55.705	7.242	1529.6	1514.17	3.504	0.402
33	1558.54	52.69	13.456	1562.39	1552.75	2.11	0.364
34	1608.69	54.232	8.227	1612.54	1585.54	5.332	0.448
35	1676.2	42.032	14.889	1689.7	1666.55	7.353	1.68
36	1697.41	50.232	9.353	1708.99	1691.63	4.486	0.667
37	1716.7	57.833	9.237	1726.35	1710.92	2.961	0.311
38	1734.06	62.836	5.779	1735.99	1726.35	1.706	0.18
39	1749.49	65.951	4.954	1753.35	1743.71	1.636	0.15
40	1761.07	70.582	2.354	1764.93	1755.28	1.404	0.066
41	1772.64	67.072	5.44	1776.5	1766.85	1.517	0.163

Fig. 5: FTIR Spectra of Optimized formula trial T-07

Table 4: FTIR peaks of Major Functional Groups

S.no	Drug	Sodium alginate	MethocelE50	Optimized formulation
1	738.6	705.97	738.76	748.41
2	1033.88	1031.95	1058.96	1161.19
3	1336.71	1327.07	1336.71	1456.3
4	1636.69	1608.69	1676.2	1761.07

The FTIR spectra of pure PROPAFENEONE and Sodium Alginate, Methocel E-15 and Optimized Formula Trial no T-07, gives us a clear picture that there is no much interaction between major functional groups between pure drug and sodium alginate and Methocel E-15.

PARTITION COEFFICIENT

The ratio of concentrations of solute in two immiscible or slightly miscible liquids or in two solids, when it is in equilibrium across the interface between them.

It is given as

$$P_{O/W} = \frac{\text{(O) organic phase}}{\text{(w)Aqueous phase}} * 100$$

Partition coefficient of the prepared microspheres is found to be 89.1%

PHYSCIAL CHARACTERSTIC PROPERTIES OF PREPARE PROPAFENONE MCROSPHERES

Table 5: Physical characterization of Propafenone microspheres

TRIALS	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Compressibility index	Hausner Ratio
Trial -1	0.7	0.6	±16.699	±40	±1.666
Trial -2	1.5	1	±14.740	±66.6	±2.994
Trial -3	2.4	2	±22.244	±33.3	±1.499
Trial -4	3	2.8	±10.076	±15.3	±1.180
Trial -5	2	1.9	±11.309	±5.26	±1.055
Trial -6	3.4	3.2	±16.699	±36.1	±1.562
Trail -7	2.6	2	±14.036	±36.8	±1.582

Fig. 6: IN-HOUSE prepared Propafenone microspheres

PERCETAGE YIELD

Table 6: Determination of percent yield from trial T-01 to T-07

TRIALS	INITIAL WEIGHT	FINAL WEIGHT	% YIELD
1	120	230	191.6
2	160	380	237.5
3	320	780	243.7
4	400	1024	256
5	480	998	207
6	420	1050	250
7	460	1006	218

The above table gives us the yield percent of Propafenone Microspheres from trial T-01 to T-07

Table 7: Percent of Propafenone release from trial T-01 to T-07

Time(M)	T-1	T-2	T-3	T-4	T-5	T-6	T-7
0	0.00	0	0	0	0.00	0	0
30	69.14	25.85	67.91	37.23	67.50	30.76	15.55
60	51.14	32.40	67.09	10.36	33.55	36.00	38.45
90	68.73	35.67	22.91	47.45	22.91	17.35	41.73
120	28.64	48.76	17.02	51.95	17.59	48.44	56.05
180	74.05	70.69	39.68	74.45	42.55	63.49	58.09
240	45.82	62.51	35.18	58.50	33.14	73.64	66.27
300	58.50	76.91	51.14	74.86	58.09	69.71	74.86
360	63.00	67.09	89.18	68.32	46.23	86.40	76.91
420	87.95	92.95	99.00	70.77	40.09	71.67	78.55
480	51.14	89.67	89.67	66.27	63.41	70.69	81.00

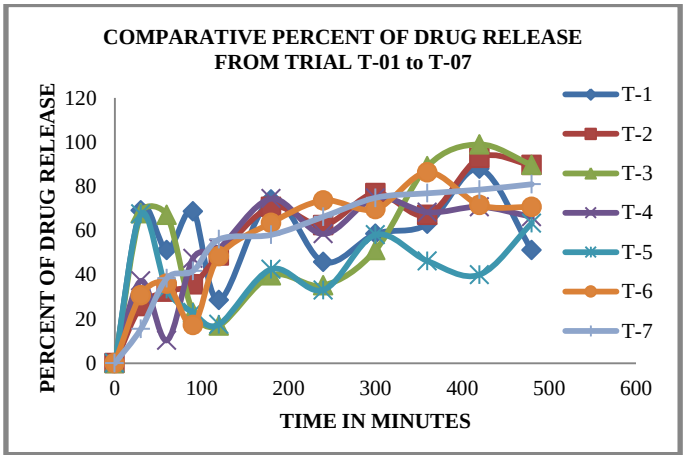


Fig. 7: comparative graphical representation of Propafenone release from trial T-01 to T-07

DETERMINATION OF ORDER OF RELEASE RATE KINETICS OF PROPAFENONE FROM OPTIMIZED TRIAL T-07

Table 8: Determination of drug release kinetics from optimized formula Trial T-07

Serial no	Zero order		First order		Higuchis model		Koresmeyer Peppas model	
	Time	% Drug Undissolved	Time	Log 100-Q	Sq. Time	Mean % Drug Dissolved	Log Time	Log Cumm. % Drug Dissolved
1	0	100	0	2.00	0	0		
2	30	89.77	30	1.95	5.48	12.24	1.48	0.47
3	60	70.14	60	1.85	7.75	25.93	1.78	1.60
4	90	62.36	90	1.79	9.49	35.83	1.95	1.89
5	120	43.14	120	1.63	10.95	49.83	2.08	2.13
6	180	37.41	180	1.57	13.42	56.85	2.26	2.29
7	240	31.27	240	1.50	15.49	67.94	2.38	2.42
8	300	25.14	300	1.40	17.32	74.74	2.48	2.52
9	360	20.64	360	1.31	18.97	76.73	2.56	2.58
10	420	19.00	420	1.28	20.49	80.34	2.62	2.63
11	480	22.68	480	1.36	21.91	79.63	2.68	2.65

GRAPHICAL REPESENTATION KINETICS OF PROPAFENONE

Release of PROPAFENONE from optimized formulation trial -07 were fitted into various kinetic models to determine the best order of release rate kinetics.

ZERO ORDER

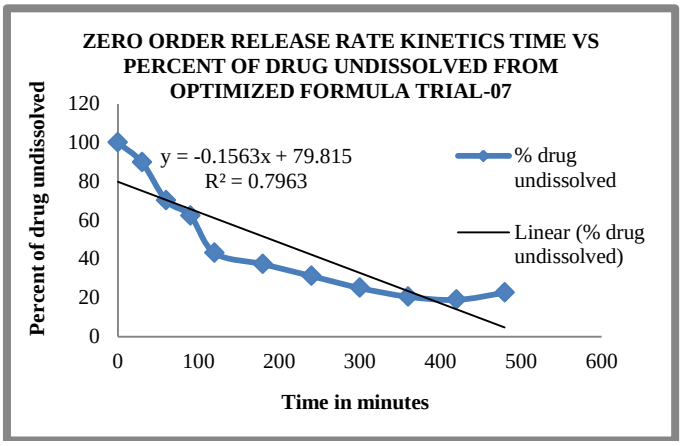


Fig. 8: zero order kinetics of Propafenone form optimized trial -07

FIRST ORDER

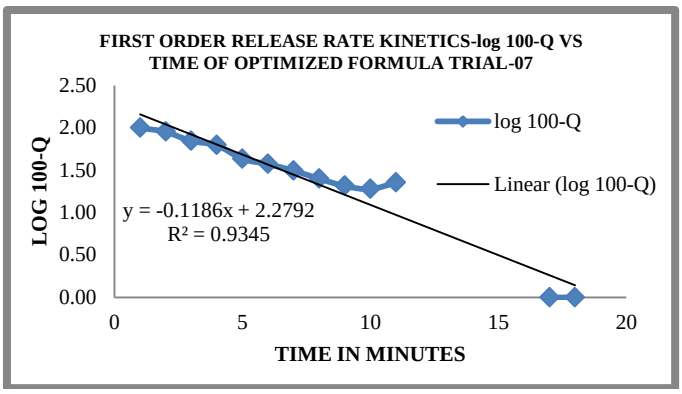


Fig. 9: First order kinetics of Propafenone form optimized trial -07

HIGUCHIS MODEL

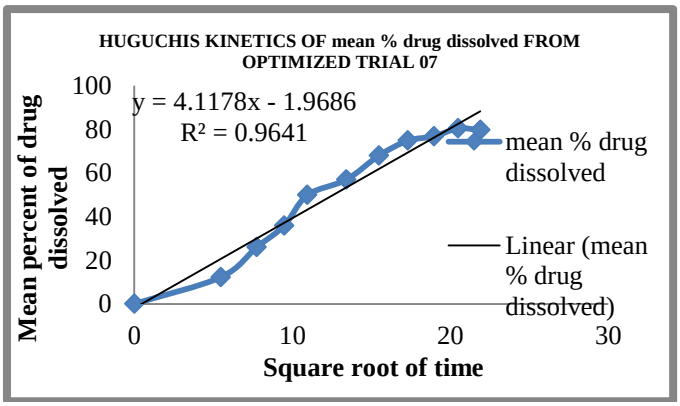


Fig. 10: HIGUCHIS order kinetics of Propafenone form optimized trial -07

KORESMEYER PEPPAS PLOT

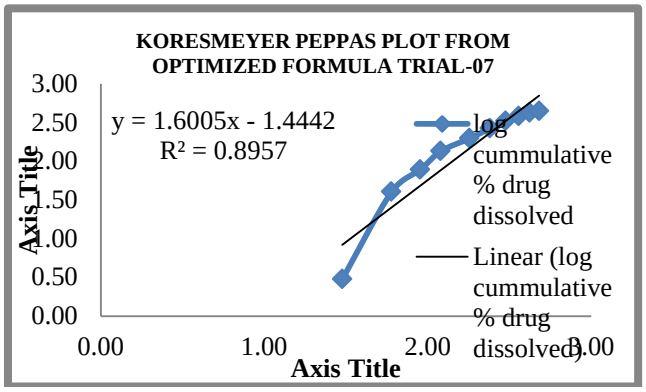


Fig. 11: KORESMEYER PEPPAS order kinetics of Propafenone form optimized trial -07

DISCUSSION

Based on the through literature survey of active pharmaceutical ingredient PROPAFENONE and excipients used in the present research work, based on it we have selected Sodium Alginate and Methocel E-15 as a release retarding agents in sustained release preparation of microspheres.

Spectrum conformation and calibration of PROPAFENONE was taken by using UV Visible Spectroscopy in 0.1N HCL at 247 nm. The regression coefficient of calibration curve was found to be 0.992.

Compatibility FTIR studies were showing no significant changes in PROPAFENONE active functional groups when spectra of FTIR run for pure PROPAFENONE and along with the excipients present in optimized formula trial T-07, similar experience was observed in case of Sodium Alginate and Methocel E-15.

Initial trial was carried out by taking Sodium Alginate along with API and calcium chloride, Sodium Lauryl Sulphate. Calcium chloride and Sodium Lauryl Sulphate was kept constant through the studies. The rate of release of PROPAFENONE from in-house prepared sustained release microspheres was found to be concentration dependent of release retarding polymers used in the present study Sodium Alginate and Methocel E-15.

Whereas constant and uniform release profile of PROPAFENONE obtained by varying the temperature, RPM, rate and time of drying from trial T-01 to T-07.

ACKNOWLEDGMENT

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