ORIGINAL RESEARCH PAPER

Pharmaceutical

FORMULATION OF NANOCAPSULATE GEL OF PARACETAMOL AND STUDYING ITS IN VITRO RELEASE PATTERN THROUGH DIFFERENT KINETIC MODELS

KEY WORDS: Franz diffusion cell, Korsmeyer Peppas, Zero order, Hixson Crowell model

Jayanti Mukherjee* Department of Pharmaceutical Chemistry, Shri Bherulal Pharmacy Institute, Indore, MP*Corresponding Author

Deepak Birla Department of Pharmacognosy, Shri Bherulal Pharmacy Institute, Indore, MP

Shivani Khoware Department of Pharmaceutics, Shri Bherulal Pharmacy Institute, Indore, MP

ABSTRACT

The paracetamol nanocapsules were prepared by the interfacial deposition technique proposed by Fessi et al using benzyl benzoate, PLGA, soyalecithin and Polaxamer. Fine concentrated colloidal dispersion of paracetamol nanocapsules were characterized by scanning electron microscopy, zeta potential and particle size analysis. The compatibility of the excipients was analysed by FTIR. The nanogel of paracetamol was formulated with carbopol 934 and triethanolamine as the major ingredients. The transdermal formulation was tested for its in vitro permeation studies through the biomimetic dialysis membrane using Franz diffusion cell. The receiver solution was phosphate buffer (pH 7.4) and the permeability study was carried out for 8 hours. The in vitro release profiles were determined by plotting cumulative % drug release Vs time (Zero order release), log cumulative % drug remaining vs time (First order release), cumulative % drug release vs square root of time (Higuchi Model), log cumulative % drug release vs log time (Korsmeyer Peppas Model) and cube root % drug remaining vs time (Hixson Crowell Model). From the release kinetics data, it was observed that the release of paracetamol from the nanocapsulate gel exhibited good correlation for Korsmeyer Peppas, Zero order, Higuchi and Hixson Crowell model.

INTRODUCTION

Drug delivery from colloidal systems such as nanoparticles or nanocapsules dispersed in a gel appears to be unique when compared to the delivery from traditional topical and dermatological formulations. Non-steroidal anti-inflammatory drugs (NSAIDS) are in use to reduce the pain and inflammation. Their main benefit derives from their anti-inflammatory and analgesic effect, but the use of these agents orally is not innocuous since their regular use may lead to chronic side effects such as gastric irritation to severe bleeding and ulceration of gastric region due to both inhibition of synthesis of prostaglandins and direct contact of the drug with mucosa. The transdermal drug delivery system of (NSAIDS) can be used to deliver drug for the treatment of acute and chronic pain.

The formulation of nanosized matter for drug delivery depends on many factors like their penetration capability through several anatomical barriers, controlled release of their active molecules and above all their stability1. Poor water solubility of paracetamol in oral dosage formulations results in low bioavailability and incomplete absorption from the gastrointestinal tract. Keeping in mind to reduce systemic side effects the present study was conducted to formulate a gel which can give more specific and localized pharmacological activity. The current approaches aim to decrease paracetamol related adverse effects like gastrointestinal disorders caused on oral administration2.

2. MATERIALS AND METHODS

2.1 Materials: All the chemicals like benzyl benzoate (Loba Chemic), soya lecithin (Hi -Media), Poloxamer 188 (Hi-Media), Carbopol 934, glycerin and triethanolamine were purchased from Loba Chemic while PLGA poly (lactic-co-glycolic acid) were purchased from Sigma - Aldrich, Switzerland. Dialysis membrane 70 MW 12,000-14,000 (Hi-Media) and the paracetamol along with organic solvents were purchased from local vendor, Indore. All the reagents and solvents were of analytical reagent (AR) grade.

2.2 Preformulation Studies

2.2.1 Determination of λmax (wavelength of maximum absorbance) for paracetamol:

A stock solution of paracetamol (1 mg/ml) was prepared by dissolving required amount of the raw drug in small amount of methanol and then diluted with distilled water. From this stock a 10 mcg/ml solution was prepared by suitable dilution with distilled water. The absorbance of the prepared solution was measured using a double beam UV (Systronic Double Beam 2203 smart) by scanning within the range of 200 to 400 nm and the wavelength of highest absorbance was determined.

2.2.2 Preparation of standard curve for pure paracetamol using UV spectrophotometer

Stock solution (1mg/ml) of paracetamol was prepared in small amount of methanol and distilled water. The stock solution was further diluted with the distilled water to achieve final concentrations of 10, 20, 30, 40, and 50 µg/ml. Each observed absorbance was plotted against concentration to prepare the standard curve of paracetamol.

2.2.3 Drug Excipients interaction studies

Fourier Transform Infrared Spectroscopy (FTIR) Vertex 70v FTIR Spectrophotometer (Bruker) was used to characterize any possible interaction between drug and excipients in the solid state3.

3. Formulation of paracetamol nanocapsules

Paracetamol nanocapsules were prepared by the interfacial deposition technique proposed by Fessi et al. The nanocapsules are essentially an oil-in-water emulsion type. 50 mg of the polymer was dissolved in 50 mL solution containing equal quantity of acetone and ethyl alcohol at stirring speed of 4000 rpm for about 30 minutes that formed the organic phase. 100 mg of soya lecithin liquid was added to the above organic phase maintaining the stirring speed for about an hour. 100 mg of the drug after dissolving in 3 mL of benzyl benzoate was then added dropwise to the above organic mixture. The stirring was maintained for about an hour. This organic mixture was then progressively added dropwise (1mL/min) through a syringe (0.22 mm) attached to a burette to distilled water (50 mL) containing poloxamer 188 as the stabilizer under constant stirring of about 4000 rpm. This was continued till a fine colloidal dispersion of nanocapsules was formed due to Tyndall effect. Organic solvent (acetone) was subsequently removed by heating

under reduced pressure. The remaining colloidal mixture was then further concentrated to about 25 mL by centrifugation (4000 rpm). The supernatant obtained was analyzed for the amount of the free drug[4].

4. Formulation of paracetamol loaded nanocapsule based gel
Required quantity of carbopol 934 was weighed and dispersed in small quantity of distilled water to prepare aqueous dispersion, and the dispersion was allowed to hydrate for 4 to 5 hours. Glycerol (10% w/w) was added subsequently to the aqueous dispersion equivalent to 1% of paracetamol into it. Triethanolamine was added in small quantity and in regular interval to the above dispersion using a magnetic stirrer with a controlled speed of 1200 rpm. Stirring was continued till the carbopol get dispersed. The gel was allowed to stand overnight to remove entrapped air5-8.

5. CHARACTERIZATION

5.1 Scanning Electron Microscopy (SEM)

SEM is a type of electron microscope utilizing the interaction of emitted electrons and atoms of a sample to collect information of the topography and other properties of the samples surface. SEM images have a characteristic appearance and are useful for judging the surface structure and topology of the sample. The surface morphology of the nanocapsules were observed using a scanning electron microscope (JEOL JSM-5600, Tokyo, Japan)[9].

5.2 Entrapment efficiency (EE %) of nanocapsules

The nanocapsule suspension was centrifuged at 4500 rpm for 1hr. The supernatant solution was separated. 1 ml of supernatant was distributed in 10 ml distilled water and the absorbance was measured using UV spectrophotometer at 266 nm using water as blank. The amount of drug entrapped was determined by subtracting amount of free drug in the supernatant from the initial amount of drug taken. The experiment was performed in three times and the average was calculated. The drug entrapment efficiency 10-11 of nanoparticles was calculated as follows:

(EE %) = (Drug given Drug loss)/Drug given × 100 %

5.3 Zeta potential measurement

The zeta potential of the synthesized nanoparticles was determined by means of NanoPlus zeta/nano particle analyzer (Malvern Instruments, United Kingdom). The measurement of zeta potential was based on the direction and velocity of particles under the influence of known electric field[12].

6. In vitro Release Study of paracetamol nanocapsule gel

The in vitro release studies were performed using modified Franz diffusion cell which consists of donor compartment, acceptor compartment, Dialysis membrane 70 (Hi-Media, Mumbai, India, MW cut-off between (12000-14000), magnetic stirrer, thermostatic water bath and sampling device13. The receptor medium was approximately 15 ml and composed of phosphate buffer saline (PBS), pH 7.4, and stirred by magnetic bar at 700 rpm to avoid different concentrations within the acceptor medium and to minimize stagnant layers 14-15. Nanocapsules based paracetamol gel (equivalent to 1 mg of drug) 16-18 was placed in the donor compartment. During the experiments, the solution in receptor side was maintained at 37 °C ± 0.5 °C. After certain time interval, 3 ml of the sample medium was withdrawn from receiver compartment through side tube and same volume of freshly prepared receptor medium were added. The samples were analyzed by UV-Vis spectrophotometer at 266 nm. For the prepared formulation, the release studies at a definite time interval were performed in triplicate[19-20].

7. Release order kinetics study

Data obtained from in vitro release studies were fitted to various kinetics models to find out the mechanism of drug release from the gel formulation. The kinetic models used were zero order, first order, Higuchi model, Korsmeyer Peppas model and Hixson Crowell model.

8. Results and Discussion:

8.1 Standard curve for pure Paracetamol using UV method:

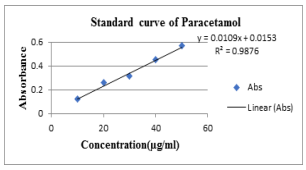


Fig 1: Standard Curve of Paracetamol

8.2 Drug Excipients interaction studies

It was revealed from the results of FTIR studies that, there were no physical or chemical incompatibilities between drug and excipients used to prepare final transdermal gel of nanocapsules.

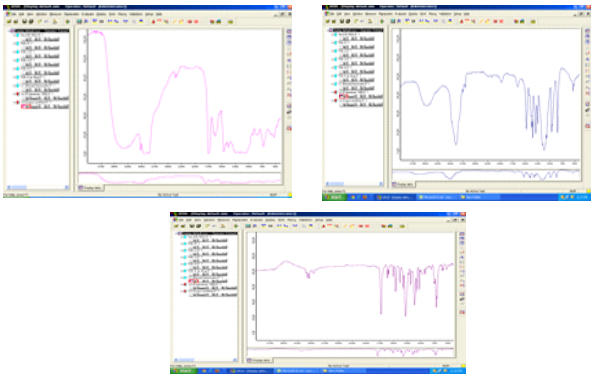


Fig 2: FTIR data of Soyalecithin, Polaxamer 188 and Benzyl Benzoate

8.3 Scanning Electron Microscopy (SEM):

Study Imaging of nanocapsules by SEM is expected to provide information on nanocapsules morphology and size. Examination of SEM photographs of the nanocapsules revealed that the surfaces were uneven and granular in structure as seen in Figure 3.

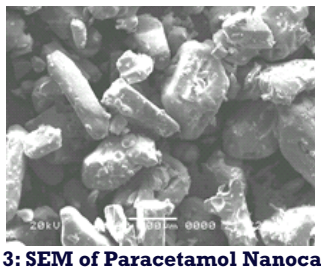


Fig 3: SEM of Paracetamol Nanocapsules

8.4 Particle size and Zeta potential measurement:

Particle size and particle size distribution are important factors in the therapeutic performance of nano formulations. From DLS measurements, individual average particle size diameter, zeta potential and polydispersity index were found to be 15802.5 nm, -9.88 and -1.426 respectively.

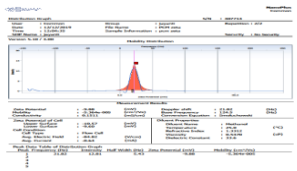


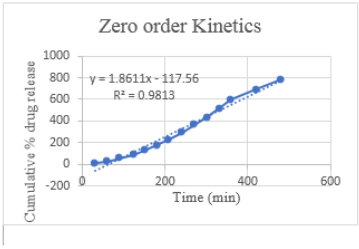
Fig 4: Zeta Potential Measurement data for Paracetamol Nanocapsules

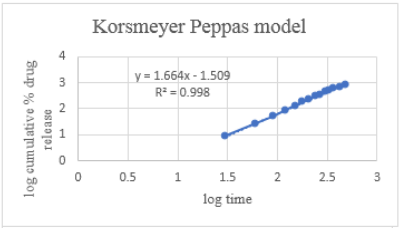
8.5 Drug Entrapment Efficiency

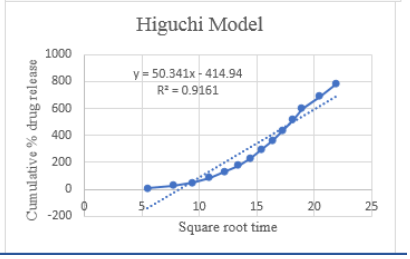
The entrapment efficiency of paracetamol in the prepared formulation was Found to be 88.6 ± 0.90

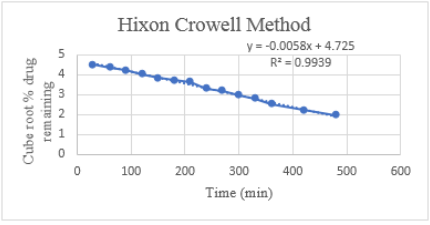
8.6 Release Order Kinetic Studies

From the release kinetics data, it was observed that the release of paracetamol from the formulated nanocapsulate gel highly correlated with Korsmeyer Peppas Model, Hixson Crowell Model, Higuchi and zero order model as evident from the value of regression coefficient.









9. CONCLUSION: The paracetamol nanocapsules were successfully developed by interfacial deposition technique. All the chemicals and the solvents used in this study were cheap and non-hazardous. Physicochemical characterization including particle size, particle size distribution, zeta potential, scanning electron microscopy and in-vitro release profile were carried out. In-vitro drug release pattern of the transdermal gel showed fast and steady state release. This steady state release can be useful to improve the penetration of drug & maintain the loading dose. Characterization of paracetamol nanocapsules reveals a good kind of product which could be reproduced for commercial purpose. Entrapment efficiency and drug release were good and up to the acceptable range.

10. Acknowledgement: The authors are thankful to Dr Amol Banerjee, Director, Dr Uday Deshpande, Dr GN Okram and Dr D M Phase of UGC-DAE Consortium, Indore for providing sophisticated instrumental facilities.

11. Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

12. Funding Sources: The authors gratefully acknowledge Madhya Pradesh Council of Science and Technology (MPCST), Bhopal, Madhya Pradesh for providing the financial grant to pursue the research project.

REFERENCES

1. Chowdary K.P.R., Rao AS. Nanoparticles as drug carriers. Indian Drugs; 1997; 34:549-556.
2. Maru S, Okaru et al. Formulation and evaluation of ibuprofen gel using a natural polymer. East and Central African Journal of Pharmaceutical Sciences, 2015; 18: 1822.
3. Nasr M, Mansour S, Mortada ND. Lipospheres as Carriers for Topical Delivery of Aceclofenac: Preparation, Characterization and In Vivo Evaluation. AAPS Pharm Sci Tech, 2008; 9(1).
4. Fessi H, Puisieux F, Devissaguet Ph, Ammoury N, Benita S. Nanocapsule formation by interfacial polymer deposition following solvent displacement: International Journal of Pharmaceutics. 1989; 55(1): R1-R4.
5. Bhalekar M R, Pokharkar V, Madgulkar A, Patil, N, Patil N K. Preparation and Evaluation of Miconazole Nitrate-Loaded Solid Lipid Nanoparticles for Topical Delivery. AAPS PharmSciTech. 2009; 10(1).
6. Lala, R.R., Awari, N.G. Nanoemulsion-Based Gel Formulations of COX-2 Inhibitors for Enhanced Efficacy in Inflammatory Conditions. Appl Nanosci. 2014; 4: 143–151.
7. Joshi M, Patravale V. Nanostructured Lipid Carrier (NLC) Based Gel of Celecoxib. Int. J. Pharm. 2008; 346: 124-132.
8. Sanad A.R., Abdelmalak N.S. Formulation of a Novel Oxybenzone-Loaded Nanostructured Lipid Carriers (NLCs). AAPS. PharmScitech. 2010.
9. Teeranachaideekul V, Boonme P et al. Influence of Oil Content on Physicochemical Properties and Skin Distribution of Nile RedLoaded NLC. J Control Release,; 2008; 128(2): 134-41.
10. Muller Goymann C.C. and, Schubert MA. Solvent injection as a new approach for manufacturing lipid nanoparticles- evaluation of the method and process parameters. Eur J Pharm Biopharm; 2003; 55: 125-131.
11. Lala, R.R., Awari, N.G. Nanoemulsion-Based Gel Formulations of COX-2 Inhibitors for Enhanced Efficacy in Inflammatory Conditions. Appl Nanosci, 2014; 4: 143–151.
12. Mazumder B, Dey S, Bhattacharya S, Sarkar S, Mohanta B. Studies on Formulation and Characterization of Cellulose-Based Microspheres of Chlorpheniramine Maleate. Arch Pharm Sci & Res., 2009; 1: 66-74
13. Kumar R., Katare O.P. Lecithin organogels as a potential phospholipid structured system for topical drug delivery: a review. AAPS. Pharm Sci Tech. 2005; 6: E298-E310.
14. Omray L.K. Formulation and characterization of liquid crystalline transdermal drug delivery system of testosterone, CTTS; 2014; 3: 1-5.
15. Omray L.K., Kohli S., Khopade A.J., Patil S., Gajbhiye A, Agrawal G.P. Development of mesophasic microreservoir based transdermal drug delivery system of propranolol. Indian J. Pharm. Sci; 2008; 70: 578-584.
16. Peppas NA., Analysis of fickian and non-fickian drug release from polymers. Pharm Acta Helv; 1985; 60: 110-111.
17. Edwards DA, Langer RA Linear Theory of Transdermal Transport Phenomena. J. Pharm. Sci., 1994; 83: 1315-1334.
18. Mario J et al; "Influence of Cyclodextrin Complexation on Piroxicam Gel Formulations"; Acta Pharm, 2005; 55: 223-236.
19. Gavini E, Sanna V, Sharma R, Juliano C, Usai M, Marchetti M, et al. Solid lipid microparticles (SLM) containing juniper oil as anti-acne topical carriers: preliminary studies. Pharm Dev Technol, 2005; 10: 479-87.
20. Sachan N K, Bhattacharya A. Modeling and Characterization of Drug Release from Glutinous Rice Starch Based Hydrogel Beads for Control Drug Delivery. Int. J. of health research. 2009; 2(1): 93-99.