PREPARATION AND EVALUATION OF LIQUID TO BE FILLED IN HARD GELATIN CAPSULE FOR INCREASING BIOAVAILABILTY OF DICLOFENAC POTASSIUM AT LOW DOSAGE

Dr. Aamer Quazi, Fayyaz Hafiz Razvi

[1] Professor, K.T. Patil College of Pharmacy, Osmanabad (M.S.), [2] Research Scientist, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (M.S.)

***Author for correspondence**

*Fayyaz Hafiz Razvi

Email id: razvi1002000@gmail.com

ABSTRACT:

Background: Diclofenac Potassium has been recently launched as low oral doses in different countries for over-the counter use. However, given the considerable first-pass metabolism of diclofenac, the degree of absorption of diclofenac Potassium at low doses remained to be determined. The aim of this study was to prepare and evaluate liquid diclofenac Potassium for hard gelatin capsule. **Methods:** The liquid for hard gelatin capsules were prepared by using PEG 400, propylene glycol and water mixture under temp of 90^0 C followed by adding PVA, Cremophore EL, Labrasol and in last diclofenac potassium finally added to the mixture under stirring. Physico-Chemical Evaluation: Pre-formulation study such as organoleptic properties were evaluated using methods such as, determination of melting point solubility, determination of λmax of diclofenac potassium, standard calibration curve of diclofenac potassium, fourier transform infra-red (FTIR) spectroscopy. Final formulations were characterized before filling into capsule for particle size and poly-dispersity index, zeta potential, determination of pH and viscosity. **Results:** The zeta potential value is -11.1 indicates ideal physical stability of prepared liquid diclofenac potassium. The pH of formulations was observed in the range of 6.7±0.43 to 7.15±0.90. Viscosity of all formulation were found in the range of 65 to 95 CPS and lying within limits from the result it was observed that viscosity increase. **Discussion**: Hence, liquid diclofenac Potassium for hard gelatin capsule can be used for lower dose and higher bioavailability to get desire pharmacological effect and with less adverse effect.

KEYWORDS: Low Doses, Diclofenac Potassium, Low Doses, Analgesic, Anti-Inflammatory, Liquid in Capsule.

INTRODUCTION:

Diclofenac potassium is a non-steroidal anti-inflammatory drug (NSAID)(1). In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and antipyretic activities. Diclofenac potassium is used in the treatment of osteoarthritis, rheumatoid arthritis ankylosing spondylitis(2).

Drug delivery systems using colloidal particulate carriers such as nanoparticles, liposomes, microemulsions and niosomes have distinct advantages over conventional dosage forms because the particles can act as drug containing reservoirs(3).

Modification of the particle composition or surface can adjust the affinity for the target site and/or the drug release rate, and slowing drug release rate may reduce the toxicity of drug. So, these carriers play an increasingly important role in drug delivery(3).

Liquid filled hard gelatin capsule are well recognized as a solid dosage form for convenient administration of drugs orally in a liquid form. Liquid filled capsule technology can be used for liquid and semisolid fills in hard gelatin or HPMC capsule with or without banding(4).

This liquid composition available help the most challenging drug compounds in capsules has increased significantly in recent years. In particular it is possible to solubilize many drug compounds in a micro emulsion pre-concentrate inside the hard gelatin capsules such that on subsequent dispersion in the gastro intestinal tract, the drug remains in solution(5–8).

It is considered that this technology can make a significant contribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in – house formulation when small quantities of drug is available(9).

Liquid-fill hard gelatin capsule technology was established in the early 1980s as an alternative to soft gelatin capsules. This technology is mostly suitable for insoluble compounds, highly potent compounds. Once the capsule is filled, they are sealed by spraying small amount of Water/ethanol mixture at the cap and body interface followed by gentle warming to fuse the two parts of capsule together or by band sealing of capsule with gelatin or cellulose(10,11).

MATERIALS AND METHOD:

MATERIALS

Diclofenac sodium was borrowed from Wockhardt Ltd., Aurangabad . Polyvinyl pyrrolidone was purchased from Moly chem, Mumbai. Polyethylene glycol (PEG) was purchased from Loba Chemine, Mumbai. Propylene glycol (PG) was purchased from Loba Chemie, Mumbai. Ethanol was purchased from Fisher scientific, Mumbai. Sodium hydroxide was purchased from Merck Specialities, Mumbai. Potassium dihydrogen phosphate was purchased from Merck Specialities, Mumbai.

METHOD

Pre-formulation Study

Characterization of diclofenac potassium was done by development of calibration curve. This was mainly done to ensure that the diclofenac potassium which is to be used of the optimum quality and its properties could be judged(12).

Organoleptic Properties

The drug sample was tested for its colour, odour and appearance(12).

Determination of Melting Point

The melting point of diclofenac potassium was determined using capillary method and checked, whether it complies with the reference standard or not(12).

Solubility

Solubility of diclofenac potassium was determined in distilled water, methanol, ethanol, DMSO, DMF. Solubility studies were performed by taking excess amount of API in different apparatus containing the solvents. The mixture was shaken at regular intervals. The solutions were filtered and analyzed spectrophoto metrically at 235nm(12).

UV Spectroscopic Analysis

Determination of λ max of Diclofenac potassium

The λmax was determined on UV spectrophotometer by using specific dilution(12).

Standard calibration curve of Diclofenac potassium

Calibration curve was prepared for the diclofenac potassium in ethanol(12).

Preparation of reagents

Preparation of working standard solution

For determining the absorbance maxima using methanol, dissolve 5 mg diclofenac potassium in 10 ml volumetric flask then take out 0.1ml upto 0.5 ml with the reagent methanol, from this sub-stock buffer prepared make dilutions in the range of lug/ml to 10 pg/ml(12).

Drug Interaction study

Fourier Transform Infra-Red Spectroscopy (FTIR)

Fourier transform infrared (FTIR) spectra were measured using an optical bench (Shimadzu FTIR 8400S, Japan) .The drug were prepared and mixed with 400 mg of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 15 tonnes pressure. It was scanned from 4,700 to 340 cm in a Shimadzu FTIR 84008 spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers that indicates incompatibility if any(12).

Preparation of liquid diclofenac potassium

Preparation of liquid formulation

To a container PEG 400 (10%), propylene glycol (10%) and water (3%) were added under stirring and heating. Product temperature was maintained at 90^0 .To the above step slowly PVA (4%) was added under stirring and product temperature was maintained at 90^0 C.To the above solution Cremophore EL (44%), Labrasol (17%) were added under stirring and heating. To the above step, Diclofenac potassium (12%) was finally added to the mixture under stirring and heating at 90^0 C(13).

Table 1: Composition of prepared liquid diclofenac potassium

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**
Diclofenac Potassium	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Propylene Glycol	21.6	21.6	40.0	21.6	21.6	21.6	21.6	21.6	21.6	21.6		21.6	21.6	21.6	21.6
PEG 400	21.6	21.6	40.0	21.6	21.6	21.6	21.6	21.6	21.6	21.6	126.6	21.6	21.6	21.6	21.6
Water	5.8	5.8	10.0	5.8	5.8	0.0	0.0	0.0	0.0	0.0			7.5	5.8	5.8
Labrasol	70.0	70.0	70.0	70.0	35.0	35.0	35.0	35.0	35.0	0.0		35.0	35.0	35.0	35.0

Gelucire 44/14	120.0	0.0	0.0	144.0	0.0	0.0	0.0	0.0	0.0	0.0					
Cremophore EL	0.0	120.0	0.0	0.0	90.0	90.0	0.0	90.0	90.0	0.0		284.2	269.8	90.0	
PVP K-30	0.0	0.0	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0					
2N Hcl	0.0	0.0	0.0	0.0	0.0	12.7	1.2	0.0	3.4	0.0	9.9				
Oleic acid	0.0	0.0	0.0	0.0	0.0	0.0	30.0	29.0	29.0	0.0					
Polysorbate 80										132.8					
HPMC/βCD											22.4	6.0			
Glycerine											79.6				
Polysorbate											11.9				
Lactic acid												6.6	12.0		
HPC SSL													7.5		
Eudragit EPO														7.5	7.5
Capmul MCM															90.0
Total	264	264	190	288	199	206	134	222	226	201	275	400	400	207	207

Characterization of prepared liquid diclofenac potassium

Particle size and polydispersity Index (PDI)

The particle size of prepared liquid diclofenac potassium was determined by using Zetasizer version 6.20 (Malvern Instruments, Malvern, UK) All the prepared batches of prepared liquid diclofenac potassium were viewed under microscope to study their size and polydispersity index (PDI). Size of liquid diclofenac potassium from each batch was measured at different location on slide by taking a small drop of prepared liquid diclofenac potassium solution on it and average size and PDI of prepared liquid diclofenac potassium were determined(14).

Zeta potential

This method is used to determine charge on prepared liquid diclofenac potassium using Zetasizer version 6.20 (Malvern Instruments, Malvern, UK). Analysis time was kept for 60 seconds and average zeta potential and charge on the prepared liquid diclofenac potassium was determined. The obtained value will be indicates that the surface of prepared liquid diclofenac potassium is dominated by the anions(14).

Determination of pH

The pH of each formulation was recorded using a calibrated digital pH meter immediately after preparation. The pH of formulations was checked and noted(14).

VISCOSITY

The viscosity of prepared liquid diclofenac potassium formulation was measured by model no LVPVE Brookfield viscometer using spindle no 61 at 100 rpm[](14).

RESULT AND DISCUSSION

Pre formulation Study

Organoleptic Properties

It is white to off-white or slightly yellowish crystalline powder.

Melting Point

The melting point of the diclofenac potassium was found to be 177±3°C, which complies with melting point reported in United States Pharmacopoeia 2011.

Solubility

Table 2: Solubility study of diclofenac potassium

Sr No	Solvent	Solubility
1	Water	Sparingly Soluble
2	Methanol	Freely Soluble
3	Alcohol	Soluble
4	Acetone.	Slightly Soluble

UV- Spectroscopic Analysis

Determination of λmax

The UV scanning of diclofenac potassium showed maximum absorbance i.e. 237.2 nm (λmax) which complies with the specification given in Indian Pharmacopoeia. The absorbance maxima for diclofenac potassium concentration was found to be 237.2 nm.

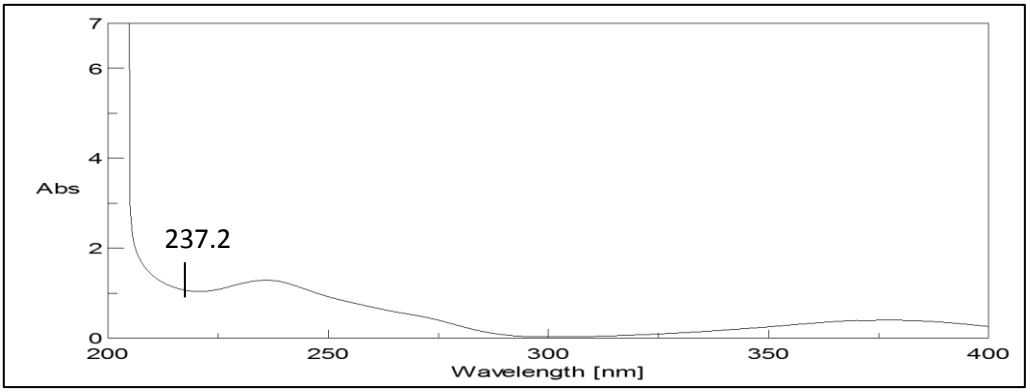


Fig 1: UV absorption spectra of diclofenac potassium

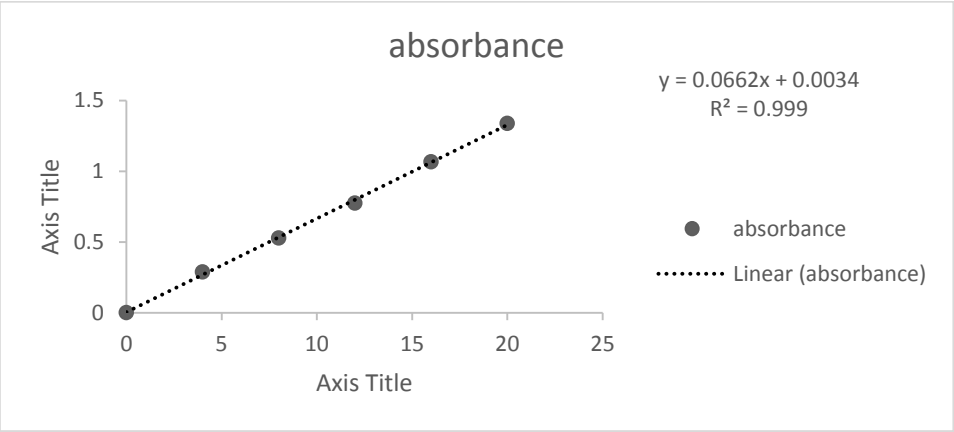
Standard Calibration Curve of diclofenac potassium

Standard calibration curve of diclofenac potassium were prepared for 4 ug/ml to 20 ug/ml concentrations in ethanol at 237.2 nm value. The absorbance v/s concentration was plotted and data was subjected to linear regression analysis. The standard calibration curve of drug in ethanol was depicted.

Table 3: Calibration curve for diclofenac potassium in ethanol

Sr No	Concentration (µgm/ml)	Absorption
1	0	0
2	4	0.2889
3	8	0.5267
4	12	0.7735
5	16	1.0676
6	20	1.3380

Fig 2: Calibration curve for diclofenac potassium in ethanol



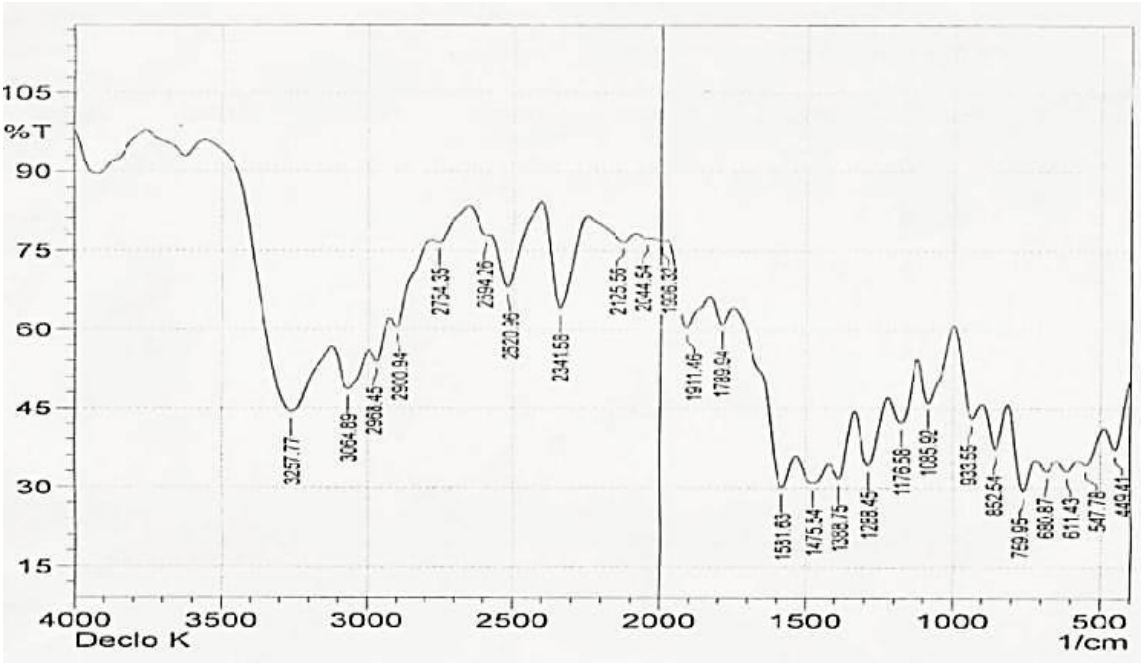
Fourier Transform Infra-Red Spectroscopy (FTIR)

Interaction study was performed with FTIR spectrophotometer with a range from 4,000 to 370 cm. The FTIR spectra of pure drug was studied. From FTIR spectra there were no disappearance characteristic peaks of the drug.

FTIR spectra of diclofenac potassium

All the prominent and primary peaks were observed in FTIR sum of diclofenac potassium and compared with the reference spectrum as per USP 2011

Fig 3: FTIR Spectra of diclofenac potassium



CHARECTERIZATION OF PREPARED LIQUID DICLOFENAC POTASSIUM

Particle size and polydispersity Index (PDI)

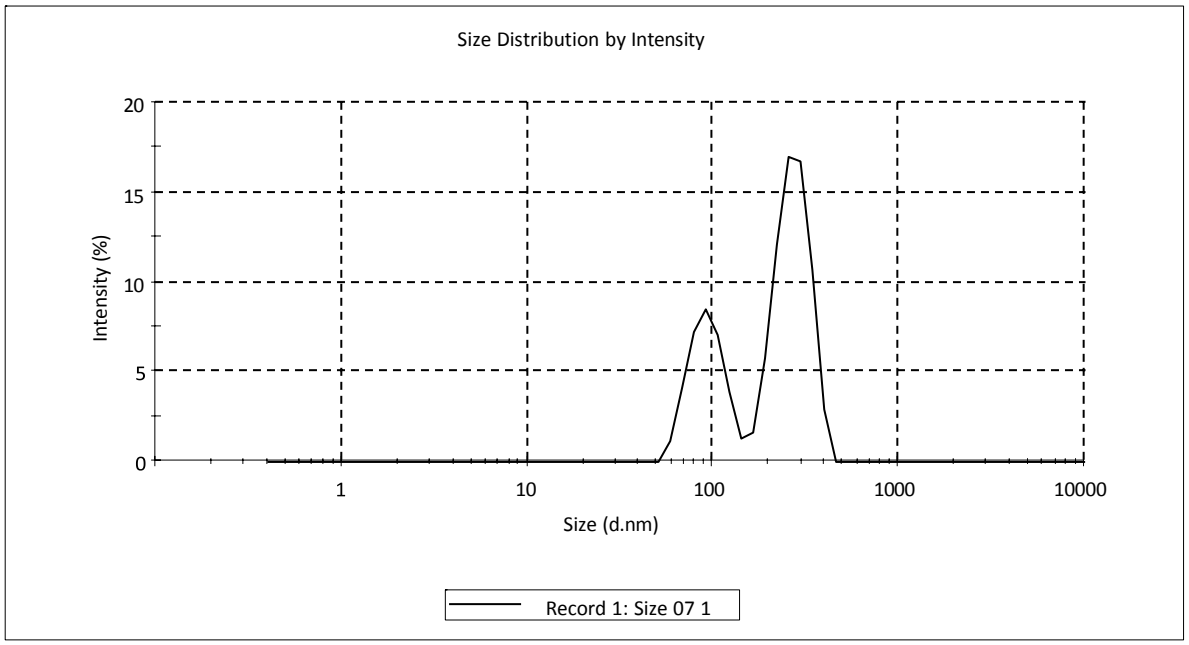


Fig 4: Particle size and polydispersity Index (PDI)

The particle size was determined by using motic microscope. All the prepared batches were viewed under microscope to study their size. All the particles were good in appearance with size particularly suitable.

Zeta potential

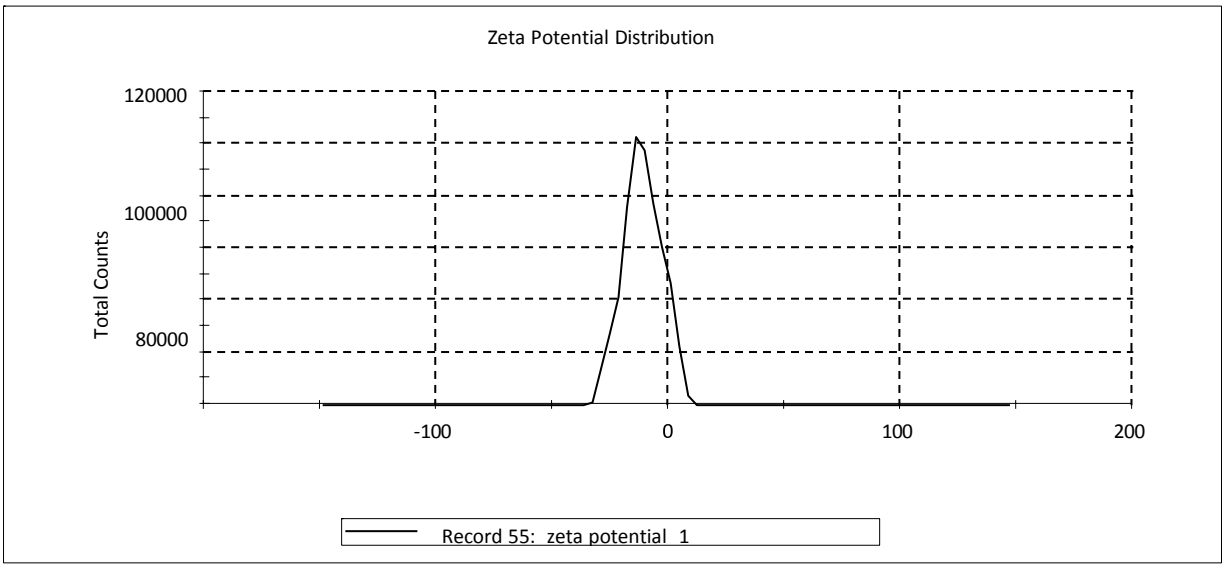


Fig 5: Zeta potential

Zeta Potential is important tool used for determination of stability and surface charges on the particles. The zeta potential value is -11.1 indicates ideal physical stability of prepared liquid diclofenac potassium.

Determination of pH

The pH of optimized formulation (F9) was recoded using a calibrated digital pH meter immediately after preparation. The pH of formulations was observed in the range of 6.7±0.43 to 7.15±0.90. The pH of all the formulation were in the desired range (6.7 to 7.4)

Viscosity:

viscosity is an expression of resistance of a fluid to flow viscosity is an important parameter for prepared liquid diclofenac potassium to be evaluated because this parameter is applicable to mixing of drug in a bulk of formulation and flow of material.

Determination of viscosity

Table 4 : Determination of viscosity

FORMULATION	Viscosity Spinder no 61 (100 rpm) CPS
F1	65
F2	68
F3	72
F4	68
F5	70
F6	75
F7	76
F8	65
F9	95
F10	66
F11	78
F12	74
F13	73
F14	69
F15	89

Viscosity of all formulation were found in the range of 65 to 95 CPS and lying withing limits from the result it was observed that viscosity increase.

DISCUSSION: Prepared and tested liquid diclofenac potassium for hard gelatin capsules. Results indicate that the formulation is ready to be filled into hard gelatin capsules. Additional research will be needed once the capsules are filled with hard gelatin. For hard gelatin capsules containing liquid diclofenac potassium, a lower dose and higher bioavailability can be used to achieve the desired pharmacological effect with fewer side effects.

CONFLICT OF INTEREST: The authors declare no conflict of interest exists.

ACKNOWLEDGEMENT: NIL

REFRENCES:

1. Moore N. Diclofenac Potassium 12.5mg Tablets for Mild to Moderate Pain and Fever: A Review of Its Pharmacology, Clinical Efficacy and Safety. Clin Drug Investig. 2007;27(3):163–95.
2. Calderon-Ospina CA, Nava-Mesa MO, Arbeláez Ariza CE. Effect of Combined Diclofenac and B Vitamins (Thiamine, Pyridoxine, and Cyanocobalamin) for Low Back Pain Management: Systematic Review and Meta-analysis. Pain Med. 2020 Apr 1;21(4):766–81.
3. Jain KK. An Overview of Drug Delivery Systems. In: Jain KK, editor. Drug Delivery Systems [Internet]. New York, NY: Springer New York; 2020 [cited 2023 Jan 25]. p. 1–54. (Methods in Molecular Biology; vol. 2059). Available from: http://link.springer.com/10.1007/978-1-4939-9798-5_1
4. Nirale P, Arora S, Solanki A, Bhat J, Singh RK, Yadav KS. Liquid Filled Hard Shell Capsules: Current Drug Delivery InfluencingPharmaceutical Technology. Curr Drug Deliv. 2022 Feb;19(2):238–49.
5. Sultana M, Sultana S, Hussain K, Saeed T, Butt MA, Raza SA, et al. Enhanced Mefenamic Acid Release from Poloxamer-Silicon Dioxide GelFilled in Hard Gelatin Capsules - An Application of Liquid Semisolid MatrixTechnology for Insoluble Drug. Curr Drug Deliv. 2022 Aug;19(7):801–11.
6. Koehl NJ, Shah S, Tenekam ID, Khamiakova T, Sauwen N, Vingerhoets S, et al. Lipid Based Formulations in Hard Gelatin and HPMC Capsules: a Physical Compatibility Study. Pharm Res. 2021 Aug;38(8):1439–54.
7. Managuli RS, Reddy MS, Koteshwara KB, Mutalik S. Enteric coating of nanostructured lipid carriers (NLCs) and enteric coating of hard gelatin capsules filled with NLCs: Feasibility studies. Pak J Pharm Sci. 2021 Jul;34(4):1323–31.
8. Jadhav S, Kaur A, Bansal AK. Comparison of Downstream Processing of Nanocrystalline Solid Dispersion and Nanosuspension of Diclofenac Acid to Develop Solid Oral Dosage Form. Pharmaceutics. 2020 Oct 23;12(11):1015.
9. Ma JH, Yang M, Zeng M, Chen XM, Lan J. [A review on liquid-filled hard gelatin capsules]. Zhongguo Zhong Yao Za Zhi Zhongguo Zhongyao Zazhi China J Chin Mater Medica. 2008 Mar;33(5):602–5.
10. Erlich L, Yu D, Pallister DA, Levinson RS, Gole DG, Wilkinson PA, et al. Relative bioavailability of danazol in dogs from liquid-filled hard gelatin capsules. Int J Pharm. 1999 Mar;179(1):49–53.
11. Barakat NS. Etodolac-Liquid-Filled Dispersion into Hard Gelatin Capsules: An Approach to Improve Dissolution and Stability of Etodolac Formulation. Drug Dev Ind Pharm. 2006 Jan;32(7):865–76.
12. Castro SR, Ribeiro LNM, Breitkreitz MC, Guilherme VA, Rodrigues da Silva GH, Mitsutake H, et al. A pre-formulation study of tetracaine loaded in optimized nanostructured lipid carriers. Sci Rep. 2021 Nov 2;11(1):21463.
13. Sonar SP, Gondkar SB, Saudagar RB. Formulation and Evaluation of Liquid Filled Hard Gelatin Capsule of Febuxostat. J Drug Deliv Ther. 2019 Sep 15;9(5):105–9.

14. Sahbaz Y, Nguyen TH, Ford L, McEvoy CL, Williams HD, Scammells PJ, et al. Ionic Liquid Forms of Weakly Acidic Drugs in Oral Lipid Formulations: Preparation, Characterization, in Vitro Digestion, and in Vivo Absorption Studies. Mol Pharm. 2017 Nov 6;14(11):3669–83.