Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v29i04.3356

FORMULATION AND EVALUATION OF FLOATING DRUGS WITH IMPORTANCE OF FLOATING DRUG DELIVERY SYSTEM

Satbir Singh[1]*, Dr Gaikwad Dushyant Dadabhau[2], Kehar Singh[3]

[1]*Research Scholar, Dept. of Pharmacy, Sun Rise University, Alwar, Rajasthan
[2]Professor, Dept. of Pharmacy, Sun Rise University, Alwar, Rajasthan
[3]Research Scholar, Dept. of Pharmacy, Sun Rise University, Alwar, Rajasthan

***Corresponding Author:-** Satbir Singh
*Research Scholar, Dept. of Pharmacy, Sun Rise University, Alwar, Rajasthan

Abstract
The development of gastro retentive dosage forms was necessitated by the need to deliver medications at a specific region of the gastrointestinal tract, the so-called absorption window. Attempts to develop gastro retentive drug delivery systems can be broadly categorized into two groups: those that rely on the natural physiology of the gastrointestinal tract and those that are intended to circumvent it. Approaches such as size or floatation, which rely on delayed stomach evacuation, are dependent on the normal physiological fed state duration of 4 to 8 hours. Low density systems that cause buoyancy (Floating drug delivery system), high density which retains the dosage form in the stomach, raft forming systems, concomitant administration of drugs or excipients which slow the motility of the gastro intestinal tract, bioadhesion to gastric mucosa, and swelling to a large size which prevent passage of dosage form through the pyloric sphincter are the primary approaches studied for gastroretentive dosage forms. Floating Drug Delivery Systems (FDDS) have a lower bulk density than gastric fluids; consequently, they float in the stomach for an extended period of time without influencing the rate of gastric emptying. While the system is afloat on the gastric contents, the drug is slowly and nearly completely released from the system at the desired rate. After the drug's discharge, the residual system becomes susceptible to stomach emptying. This causes an increase in gastro retentive time, bioavailability, and improved control of plasma drug concentration fluctuations. Thus, the floating drug delivery system is a safe and effective drug delivery technology.

Key words: Formulation, evaluation, floating, drug delivery system.

1. INTRODUCTION

Oral administration is the most effective and convenient method of drug administration. The conventional immediate release system accomplishes and maintains therapeutically effective drug concentrations, but these formulations must be taken multiple times daily. This leads to significant fluctuations in plasma drug levels, and the administration frequency results in patient noncompliance. Recent technological advances in the pharmaceutical industry have resulted in the development of numerous novel drug delivery systems that have the potential to revolutionize the method of medication administration and provide a variety of therapeutic benefits. [1]

Oral drug delivery is the most common method of drug administration among those that have been studied for systemic drug delivery via pharmaceutical products of various dosage forms. The oral

route is considered the most natural, convenient, and secure due to its simplicity of administration, patient acceptance, and efficient manufacturing process.

Pharmaceuticals intended for oral administration frequently employ conventional or instant-release drug delivery methods, which are designed for rapid drug release and assimilation. These formulations of immediate release doses are subject to certain restrictions, including:

- Short half-lives necessitate frequent administration, increasing the risk of missed doses and decreasing patient compliance.
- The plasma concentration-time profile is often peak-valley, making it difficult to achieve steady state.
- As the steady state concentration values fall or rise outside the therapeutic range, fluctuations in the drug concentration may result in under- or overmedication. [2]

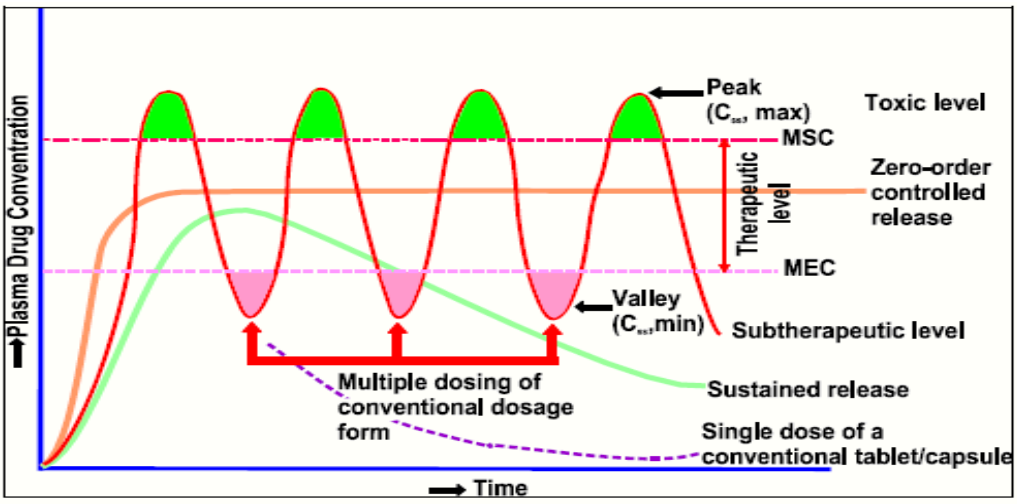


Figure: 1: A plasma concentration time profile

In an effort to provide a single dosage therapy for the duration of treatment, controlled or sustained release medication delivery systems have garnered significant interest. These delivery methods offer several advantages over conventional methods, such as increased efficacy, single-dose therapy with reduced toxicity, and increased patient convenience. The primary objective of controlled drug delivery systems is to enhance the efficacy of medication therapy.
In order to control the rate of drug delivery, prolong the therapeutic effect, and/or target drug delivery to a specific tissue, controlled drug delivery systems have been developed.[3]

The selection of a drug delivery system is a crucial aspect of any research. In this study, we utilized multiple methods for the development of various delivery systems. The following are:

- Effervescent floating tablets
- Mucoadhesive tablets
- Standard matrix tablet
- In-place gel

1.1 FLOATING DRUG DELIVERY SYSTEM (FDDS)

Because floating drug delivery systems (FDDS) have a lower bulk density than gastric fluids, they can float in the stomach for an extended period of time without impeding the stomach's emptying rate. The medication is withdrawn from the system at the desired rate while the body floats on the stomach's contents. The residual system of the stomach is emptied after medication discharge. As a result, the GRT is increased and plasma drug concentration fluctuations are better managed. [4]

1.2 APPLICATIONS OF FDDS

1.2.1 LONG-TERM DRUG DELIVERY

Since the HBS system can remain in the stomach for extended periods, it can progressively release the medication. Consequently, these technologies can address the problem of a brief gastric residence time associated with oral controlled release formulations. These systems can levitate on the stomach's contents due to their high bulk density.

1.2.2 SPECIFIC SITE DRUG DELIVERY

These systems are particularly advantageous for medications, such as riboflavin, furosemide, and misoprostol that are specifically absorbed from the stomach or proximal small intestine.

1.3 IMPROVEMENT OF ABSORPTION

Medications with limited bioavailability due to site-specific absorption from the upper section of the GIT are potential candidates for formulation as floating drug delivery systems. This would increase their rate of absorption.

1.4 MAINTAINING A CONSTANT BLOOD PRESSURE

This makes it easy to maintain a constant blood level while also simplifying administration and enhancing patient compliance. [5,6]

1.5 ADVANTAGES OF FDDS

- This system is advantageous for medications that are absorbed in the intestines.
- Aspirin and other acidic compounds irritate the stomach lining when they come into contact with it (e.g. ferrous salts, antacids).
- Drugs intended for local action in the stomach, such as antacids, benefit from this system. [7]

1.6 EFFERVESCENT FDDS

These effervescent drug delivery systems employ expandable polysaccharide matrices, such as chitosan or methocel.

Due to the acidity of the gastric contents, carbonates (such as sodium bicarbonate) and other organic acids (such as citric acid and tartaric acid) present in the formulation produce carbon dioxide (CO_2) gas, which is then trapped in the gelling hydrocolloid, reducing the system's density and causing it to float on the gastric fluid. [8]

Incorporating a matrix with a liquid component result in the production of a gas that evaporates at body temperature. This system is categorized as follows.

- Gas generating systems
- Volatile liquid/Vacuum containing systems

Gas – Generating System:

These systems consist of two layers surrounding sustained release capsules that serve as "seeds." The innermost layer consists of effervescent agents, while the outermost layer consists of layers of swellable membranes. The system immediately sinks when immersed in a dissolving liquid at body temperature, then generates enlarged tablets that resemble balloons and float due to their reduced density. This reduced density is caused by the production and sequestration of CO_2 within the system. [9]

1.7 THE BENEFITS OF THIS TECHNOLOGY

- Excellent bioavailability
- Issues of incompatibility and stability can be resolved. Elegance to the item
- Enhanced product reliability Very little incompatibility [10]

1.8 OVERVIEW OF IN SITU CREATING GEL

Preformed polymers continue to have limitations that may discourage their use for ophthalmic drug delivery or tear replacement. They prevent the precise and repeatable administration of medication concentrations, and after administration they frequently cause blurred vision, eyelid crusting, and tears. A novel approach is to combine the advantages of solutions and gels, such as the precision and simplicity of administration of solutions and the prolonged residence time of gels.

A novel approach is to combine the advantages of solutions and gels, such as the precision and simplicity of administration of solutions and the prolonged residence time of gels. Sol to gel transformation by a variety of mechanisms is as follows:

- pH-sensitive gel-forming apparatus
- Ion-sensitive gel-forming apparatus
- Temperature-sensitive gel-forming apparatus [11]

1.9 Method for pH-dependent polymer formation

The use of pH-sensitive gel formation systems as intelligent materials for various biomedical applications has been the subject of extensive research. These systems expand or contract in response to changes in pH. When the oral delivery is pH-sensitive, oral medications can be administered using pH-sensitive methods. The swelling of the pH-sensitive polymer system is dependent on alterations in the gastrointestinal tract's natural pH environment, which ranges from acidic in the stomach to neutral in the intestine. Consequently, these systems permit the discharge of a bioactive substance at a specific location. They might mitigate adverse effects while enhancing pharmacological response.

1.10 Method for producing Ion-sensitive polymer

Ion sensitive gel forming systems are a novel type of gel in which a polymer solution containing a substance gels upon contact with a specific ion at a specific site. This gel-forming system for ionic-trigger-based site-specific drug delivery is efficacious. [12,13]

2. RESEARCH METHODOLOGY

2.1 Preformulation study and analytical method for HZH

% Purity HZH

Shake for 15 minutes a portion of the pulverized tablets that contain 30 mL of methanol and 50 mg of hydralazine hydrochloride. Then, filter and add enough methanol to make 50 mL. One volume of filtrate should be diluted with 50 volumes of water. Using a double beam UV/Vis spectrophotometer, the absorbance of the filtrate at a maximal wavelength of 265 nm was measured. [14]

2.2 Formulation and Assessment of HZH Floating Tablets

Drug-excipient compatibility investigation for HZH floating tablets

• DSC

Differential scanning calorimetry (DSC) was employed with the Perkins Elmer, Pyris DSC model under nitrogen flow to assess the compatibility of the drug with the excipients. In aluminium DSC trays placed in the DSC cell, 10mg of each sample, including the drug, the drug combined with each excipient, and a mixture of the drug and excipients, was precisely weighed and sealed. The conventional method for estimating temperature and enthalpy was utilized, with the liquefaction of purified indium metal serving as the standard. From 25 to 300 degrees Celsius, DSC experiments were conducted at 10 degrees Celsius with a nitrogen flow rate of 40 ml/min. An empty aluminum skillet was used as a standard. [15]

FTIR

Similar to DSC, the FTIR-Bruker alpha-E model was utilized to capture the IR spectra of the drug, drug + each excipient, and drug and excipient mixtures in order to identify any incompatible peaks. Three trial batches FLT1, FLT2, and FLT3 were formulated and the concentrations of various polymers were determined based on the results obtained in order to achieve the best possible results. [16]

2.3 Method for manufacturing preliminary trial batches of Floating tablets

- Pure HZH, release-retarding polymers (HPMC K4M and Carbopol 940), and gas generating agent (Na2CO3) were mixed using a mortar and pestle. The mixture was created by combining all ingredients, which was then granulated. Mixing starch and water produced the binding paste.
- Upon attaining granule, the granulated blend was discharged from the RMG and passed through a 30# sieve to obtain uniform-sized granule before being dried.
- The desiccated mixture was passed through a 40# sieve and lubrication was applied.
- After passing lubricating material through a 40# and 60# sieve, it was added to the mixture. This mixture was subjected to geometrical blending to ensure uniformity. [17]

This mixture was compacted with 5.0mm S/C punches. Evaluation of floating tablet trial lots Test for dissolution (In-Vitro release)

The dissolution parameter for trial samples was measured to determine the cumulative percentage of drug release. Observe the following parameters and procedures:

Study of buoyancy in vitro

The tablets are able to float due to the low density, swelling capacity, and gas production of HPMC with sodium bicarbonate. After being immersed in 0.1N HCl at 37^0C, the granules float and remain buoyant. Within 5 to 20 seconds, all tablets float atop the water. Several batches of floating tablets had an outstanding floating duration, or a floating time of more than 20 hours, according to the findings. This could be due to the amount of hydrophilic polymer present.

The method: The floating behavior of the granules was observed in triplicate. A tablet was deposited in a glass beaker containing 200 mL of 0.1 N HCl at 37 0.5 degrees Celsius. We measured total floating time (TFT) and floating latency time (FLT).

Sustained stability

This investigation was conducted to evaluate the formulation's consistency. Three months were spent storing the Optimized batch's tablets at 40^0C and 75% RH. The tablet samples were collected at regular intervals of 2, 4, 8, and 12 weeks, and any significant differences in the parameters were evaluated. Using an ultraviolet spectrophotometer, the potency of the withdrawn samples was measured. When p 0.05, the result was considered significant. [18]

2.4 Experimental design for the optimization of HZH floating tablets

In order to manufacture the final batch of floating tables, preliminary trial batches FLT1-FLT2-FLT3 were subjected to experiment design, and the final 15 batches were formulated using Box-Behnken design. [19]

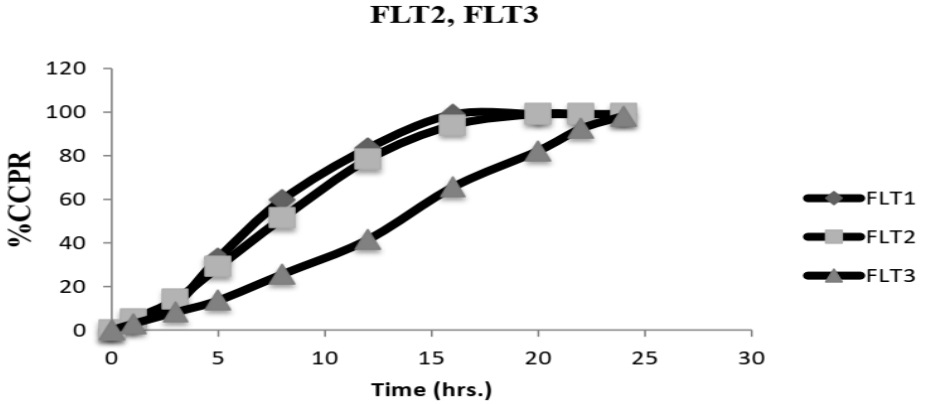
3. RESULTS AND DISCUSSION

a. A drug-excipient compatibility research was conducted for HZH floating tablets using DSC and FTIR in order to investigate and identify incompatibilities The results of these in-vitro dissolution investigations are depicted in Table-1.

Table-1: *Cumulative percentage release of floating trial batches (n=1, mean ± SD)*

TIME (hrs.)	Cumulative percentage release of HZH		
	FLT-T1	FLT-T2	FLT-T3
0	0±0.00	0±0.00	0±0.00
1	3.01±0.09	5.01±0.10	2.95±0.11
3	11.99±0.10	13.99±0.13	8.26±0.12
5	32.99±0.08	29.03±0.10	13.65±0.13
8	59.81±0.11	51.34±0.12	25.65±0.09
12	83.32±0.11	78.19±0.11	41.48±0.07
16	98.91±0.09	93.97±0.12	65.61±0.13
20	99±0.11	99.1±0.11	82.25±0.18
22	99±0.11	99.1±0.10	92.38±0.11
24	99±0.11	99.1±0.11	98.22±0.12

Figure-2 Cumulative percent release graph for floating trial batches Chart Cumulative percent release profile of FLT1,FLT2, FLT3



In comparison to the other two trial batches, batch FLT3 (HPMC K4M+Carbopol 940) exhibited the desired release profile of HZH up to 24 hours, as shown in the graph. Consequently, a mixture of HPMC K4M and Carbopol 940 was chosen for further optimization using experimental design.

Ready for compression characterization powder mixture

All of the aforementioned parameters were evaluated for each optimization run. Table-2 contains the study's findings.

Table 2 Evaluation of the compressed powder combination

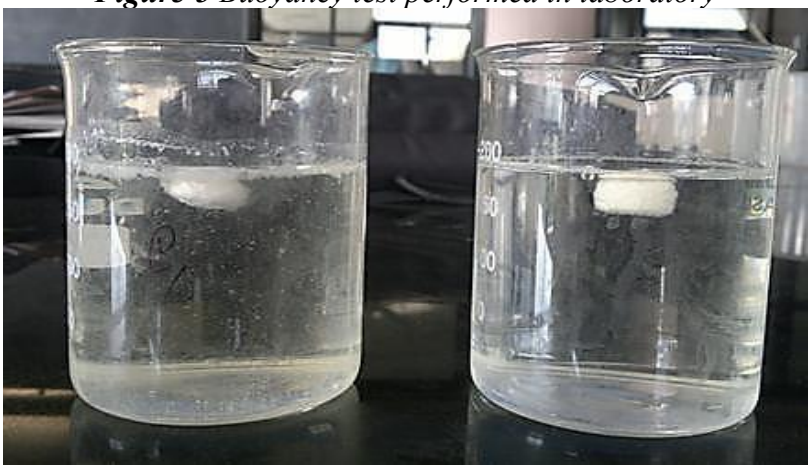
Batch no.	Angle ofrepose	Bulk density(g/cm^3)	Tapped density(g/cm^3)	% compressibility
FLT-1	24.83±1.34	0.27±0.4	0.32±0.4	15.62
FLT-2	26.20±1.24	0.28±0.2	0.32±0.5	12.50
FLT-3	27.36±1.44	0.27±0.4	0.33±0.3	12.12
FLT-4	26.25±1.23	0.27±0.3	0.31±0.3	12.90
FLT-5	25.45±1.56	0.28±0.4	0.32±0.2	15.15
FLT-6	26.71±1.33	0.27±0.3	0.33±0.2	15.62
FLT-7	25.92±1.55	0.26±0.3	0.31±0.3	13.12
FLT-8	25.81±1.48	0.27±0.2	0.32±0.4	15.62
FLT-9	26.14±1.62	0.28±0.3	0.34±0.4	15.64
FLT-10	26.55±1.25	0.29±0.2	0.34±0.2	14.70
FLT-11	24.96±1.34	0.27±0.4	0.32±0.2	12.50
FLT-12	25.12±1.45	0.28±0.3	0.32±0.3	15.15
FLT-13	25.48±1.38	0.27±0.3	0.32±0.3	15.91
FLT-14	25.98±1.56	0.28±0.4	0.33±0.2	15.15
FLT-15	25.81±1.72	0.27±0.4	0.32±0.2	15.62
(n=3, mean ± SD)				

As shown in the table, the angles of repose for all batches ranged from 24.21 to 26.71 degrees, indicating satisfactory flow characteristics. The compressibility indices of all samples, which range from 12.12% to 15.91%, indicate excellent compressibility. Consequently, each optimization batch exhibited superior flow and compressibility, which is advantageous for direct compressible tablets.
The results of these experiments on the weight variation, thickness, hardness, friability, assay, T90, T20, and Q1 of tablets prepared from all optimization batches are presented.
The test for weight variation was conducted by weighing 20 tablets individually, and it was determined that all formulation weights fell within the range of 280 mg, which was within the pharmacopoeia's restrictions; therefore, the test for weight variation was successful for all pills. All of the tablets had uniform weights with minor standard deviations.
All tablet batches had mean tablet thicknesses ranging between 3.95 and 4.01 mm. Consequently, these data reveal batch-to-batch and within-batch size consistency.
The hardness of tablets from samples that were optimized was between 4-5 kg/cm^2. This ensures that all quantities have excellent handling characteristics.
To ensure that the tablets were mechanically resistant to stress and vibration, the percentage of friability was calculated, and the results for each optimized batch were less than 1%.
The drug content of all samples ranged from 95.07% to 108.1%, which is within the acceptable range and suggests that each batch received the same dose.

Table3 *Evaluation of floating tablets (FLT1-FLT15)*

BatchNo.	Tablet Thickness (mm)	Tablet Hardness (kg/cm3)	Averagetablet wt.(mg)	Tab. Friability (%)	Drug content(%)
FLT-1	3.89±0.05	4±0.01	280	0.63±0.01	98.22±0.57
FLT-2	3.98±0.04	5±0.02	280	0.7±0.01	99.51±0.57
FLT-3	4.01±0.05	4±0.01	280	0.66±0.01	106.2±0.57
FLT-4	3.96±0.05	4±0.03	280	0.7±0.01	99.75±0.57
FLT-5	4.01±0.05	5±0.01	280	0.7±0.01	99.15±1
FLT-6	4.01±0.05	4±0.02	280	0.74±0.01	98.11±0.57
FLT-7	3.99±0.06	4±0.15	280	0.77±0.02	98.6±0.57
FLT-8	3.86±0.05	5±0.01	280	0.69±0.02	99.72±0.52
FLT-9	4±0.05	4±0.02	280	0.7±0.01	99.51±0.57
FLT-10	3.98±0.06	4±0.02	280	0.7±0.01	99.51±0.57
FLT-11	3.98±0.05	5±0.01	280	0.78±0.01	98.10±0.57
FLT-12	3.98±0.05	5±0.02	280	0.7±0.01	99.51±0.57
FLT-13	3.99±0.05	4±0.01	280	0.7±0.01	98.97±1
FLT-14	4.01±0.05	4±0.01	280	0.81±0.01	99.46±0.57
FLT-15	3.98±0.05	4±0.11	280	0.77±0.01	99.74±1
n = 3, (Average ± SD)					

Figure-3 *Buoyancy test performed in laboratory*



CONCLUSION

Hydralazine is used to treat hypertension by functioning as a vasodilator primarily in the arteries and arterioles. The half-life of Hydralazine HCl is only 2 to 3 hours, and it is administered 3 to 4 times per day. Therefore, patients require frequent dosage, and missing doses may result in chronic symptoms. Long-acting oral dosage forms that can continue to release the drug at a controlled rate for a predetermined period of time can be administered to avoid frequent administrations. Therefore, to improve patient compliance, the sustained release oral floating dosage form may be a useful option, as it can deliver the drug continuously at a controlled rate without the need for frequent dosing with tablets. This would increase patient adherence and enhance the treatment or therapy. The formulation of hydralazine hydrochloride was made by combining the substance, HPMC, Na2CO3, Sodium Alginate, Carbopol 940, Gellan gum, and diluents using various formulation techniques. The matrix tablets expanded in the presence of the aqueous medium. According to the hypothesis, tablets formulated with HPMC, sodium alginate, and sodium bicarbonate demonstrated excellent drug retention and buoyant properties. The formulation containing xanthan gum demonstrated inadequate drug retention. While investigating various formulations, both favorable and unfavorable outcomes were discovered. According to predetermined evaluation parameters such as In-vitro dissolution, tablet adhesion rate, tablet floating duration, etc., the results were accurately evaluated. The most effective formulations were retained for stability testing and were found to be stable under a variety of conditions. The quantities CP-1 that were manufactured using DOE software and optimized. These samples were then compared to the final batch of the formulation, and nearly identical results were observed. The formulation was determined to be stable under both normal and accelerated conditions.

As a result of this research, it has been determined that the final formula and process satisfy the majority of the desired characteristics. The selected excipients were highly compatible with the drug, and their concentrations were adjusted to achieve the desired release profile. The adhesion rate and desired release profile of floating effervescent tablets were superior to those of other dosage forms. The procedure was reproducible, efficient, reliable, and economical.

REFERENCES

1. Arnold DR, Granvil CP, Ward KW, Proksch JW. Quantitative determination of Besifloxacin Hydrochloride, a novel fluoroquinolone antimicrobial agent, in human tears by liquid chromatography-tandem mass spectrometry. J Chromatog B 2008; 867:105-110.
2. Balzli CL, Caballero AR, Tang A, Weeks AC, O´Callaghan RJ. Penetration and effectiveness of prophylactic fluoroquinolones in experimental methicillin- sensitive or methicillin-resistant Staphylococcus aureus anterior chamber infections. J Cataract Refract Surg. 2010; 36:2160–7.
3. Biju SS, Talegaonkar S, Mishra PR and Khar RK. Vesicular systems: An overview. Indian Journal of Pharmaceutical science. 2006; 68(2):141-153.
4. Chitra G, Vijay J, Upendra N. Formulation and optimization of thermosensitive in- situ gel of moxifloxacin Hydrochloride for ocular drug delivery. IJPPS. 2018; 10(3):123-130
5. Draize, John H., Woodard, Geoffrey and Calvery, Herbert O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. Journal of Pharmacology and Experimental Therapeutics. 1944; 82: 377- 390.
6. Engels T, Forster T, Rybinsko WV. The influence of coemulsifier type on the stability of oil- in-water emulsions. Colloids Surf A Physicochem Eng Aspects. 1995; 99:141– 9.
7. Gunashekar GS, Krishna M. An Overview on Powder X-Ray Diffraction and HaBe A, Keipert S. Development and characterization of microemulsions for ocular application. Eur J Pharm Biopharm. 1997; 43:179–83.
8. Higuchi T: Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci. 1961; 50: 847-875.
9. Hixson AW and Crowell JH. Dependence of Reaction Velocity upon surface and Agitation.

10. Hossain A, Alam S, Paul P. Development and Evaluation of Sustained Release Matrix Tablets of Indapamide using Methocel K15M CR Md. Journal of Applied Pharmaceutical Science. 2013;3(5):85-90
11. Huibers PD, Shah D. Evidence for synergism in non-ionic surfactant mixtures: enhancement of solubilization in water-inoil microemulsions. Langmuir. 1997; 13:5762–5.
12. ICH Harmonised Tripartite Guideline. Validation of Analytical Procedures: Text and Methodology Q2(R1). Available at: < http://www.ich.org/home.html >. Accessed on: 11 Nov 2016.
13. Its Current Applications. Research & Reviews: Journal of Physics. 2015; 4 (3):6- 10. Kawakami K, Yoshikawa T, Hayashi T, Nishihara Y, Masuda K. Microemulsion formulation for enhanced absorption of poorly soluble drugs. II. In vivo study. J Control Release. 2002; 81:75–82.
14. Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. IJP. 1983; 15: 25-35
15. Kumar S, Kumar M, Majumdar DK, Sharma PK, Singh CL, Singh A. Development and Validation of Different Ultraviolet-Spectrophotometric Methods for the Estimation of Besifloxacin Hydrochloride in Different Simulated Body Fluids.
16. Márcia CN Costa, Amanda T Barden, Juliana MM Andrade, Tércio P Oppe, Elfrides ES Schapoval. Quantitative evaluation of Besifloxacin Hydrochloride ophthalmic suspension by HPLC, application to bioassay method and cytotoxicity studies.
17. Mohamed Firthouse PU, Mohamed Halith S, Wahab SU, Sirajudeen M,, Mohideen SK. Formulation and Evaluation of Miconazole Niosomes. International Journal of Pharm Tech Research. 2011; 3(2): 1019-1022.
18. Ninham BW, Chen SJ, Evans DF. Role of oils and other factors in microemulsion design. J Phys Chem. 1984; 88:5855–7.
19. OECD Guideline for testing of chemicals No. 405. Acute eye irritation/corrosion. Paris, France: OECD; 2012.