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Evaluation of Capsule-Fillable Liquids with Solubilizers: Gelucire, Cremophore, and PVP K-30 - A Physicochemical Study

Aamer Quazi[1], Razvi Fayyaz Hafiz[2*], Rohit Patil[3], Dinesh Nalage[4], Shaikh Mohammad Azhar Husain[5]
[1]Dept. of Pharmacy, K.T. Patil College of Pharmacy, Osmanabad, Maharashtra, India
[2] Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India
[3]Dept. of Botany, Government Institute of Science, Aurangabad, Maharashtra, India
[4]Dept. Molecular Biology and Microbiology, One Step Molecular diagnostic, Aurangabad, Maharashtra, India
[5]SSJP R.P. College of Pharmacy, Alni, Osmanaba, Maharashtra, India
***Corresponding author**: Fayyaz Razvi.
Email ID: razvi1002000@gmail.com, Mobile: +91 9700808582

ABSTRACT
The aim of this study was to create an immediate release dosage form using different solubilizers in hard gelatin capsules and evaluate their effects on physicochemical characteristics. Gelucire, Cremophore, and PVP K-30 were used as solubilizers to increase solubility, and an anti-inflammatory drug was used as a model drug. Excipients such as Low-Viscosity Hydroxypropylcellulose, Cremophore EL, and hydrochloric acid were also used. The final formulation was studied for in-vitro and stability studies. Parameters such as clarity/turbidity, weight variation, leakage, density, viscosity, disintegration, and dissolution were evaluated. The formulations with Gelucire and Cremophore EL showed better results in the in-vitro dissolution-release study using a paddle apparatus and were stable for 3 months in a stability chamber at 400C/75% RH. However, the PVP K-30 formulation showed a better release rate but was unstable and caused capsule deformation within 1 month during the stability study.
Keywords: *Solubilizers, Hard gelatin capsules, Immediate release, Anti-inflammatory, Stability study*

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INTRODUCTION

Diclofenac, also known as 2-[(2,6-dichlorophenyl) amino] benzene acetic acid, monopotassium salt, is a widely used anti-inflammatory drug worldwide[1]. It is highly effective in treating inflammation-related conditions such as flush flare and wheal[2]. The drug was chosen for arthritis and anti-inflammatory studies[3]. The drug works by inhibiting the cyclooxygenase 1 and 2 pathways and has a limiting effect on the arachidonic acid pathway[4]. Diclofenac is available in different formulations, and there is a need to develop new approaches to enhance its speed and efficacy in relieving pain[5]. Diclofenac is commonly used to treat musculoskeletal pain, joint disorders, various types of arthritis, and cramps[6]. It also exhibits analgesic and antipyretic properties. Diclofenac potassium is 100% absorbed after oral administration, making it suitable for flexible dosing regimens[7]. Nevertheless, only approximately 50% of the absorbed dosage is systemically accessible because of first-pass metabolism.The medication is more than 99% bound to human blood proteins, principally to albumin, and has an apparent volume of distribution of 1.3 L/kg[8]. Since diclofenac diffuses into and out of the synovial fluid, it is unclear if this affects how effective it is[9]. Developing a liquid capsule as an immediate release formulation can provide faster and more effective concentrations of diclofenac, leading to a lower and more prolonged excruciating effect. The formulation may also help to reduce drug loss during pharmacokinetics action, mainly during its absorption stage, resulting in a direct effect on absorption and effectiveness on target sites[10,11]. This new formulation could reduce inter and intra-subject variability and improve the drug's overall efficacy.

MATERIAL AND METHODS

To create a trial batch of Diclofenac Potassium, the liquid was adjusted to a pH of 6.7 to 6.8 using 2N HCl. HPMC-based capsule shells were used, and the same ingredients were used for all formulations, except for

the solubilizers. Gelucire, Cremophore, and PVP K-30 were used as solubilizers for the respective formulations, and the only difference in the process was the use of different solubilizers in the third step.
To make the formulation, a 100ml stainless container was used, and a weighed quantity of propylene glycol was added and stirred using a hot plate, with the temperature maintained at around 50°C. Then, a weighed quantity of PEG 400 was added and stirred for 2 minutes, with the temperature maintained at around 50°C. After that, the mixture was added with a weighed quantity of Gelucire, Cremophore, or PVP K-30, respectively, based on the formulation with different solubilizers. The addition was done under stirring and maintaining the temperature at around 50°C, and the product was stirred for an additional 2 minutes after mixing. Next, a weighed quantity of Labrasol was added under stirring and heating, and Diclofenac Potassium was slowly added under heating and stirring until a clear solution was obtained. The mixture was then allowed to cool at room temperature, and pH adjustment was done using 2N HCl.
Finally, the clear solution was filled into empty capsule shells, and a red-colored band seal was done. These band-sealed capsules were then analyzed.

RESULTS AND DISCUSSION

The physicochemical properties of all the liquid-filled capsules were examined, including clarity/turbidity of the solution, weight variation, leakage test after band sealing, density and viscosity of the solution, disintegration test, and dissolution test. The disintegration test was conducted to confirm that the dosage form disintegrated within the expected time frame. The formulation was placed in a basket apparatus with a buffer system, and the drug release and absence of capsule or band material residue were evaluated. The disintegration test apparatus consisted of a beaker with six baskets, and the capsules were placed in individual baskets above the mesh. The test was repeated for 18 capsules, and the capsules cleared the capsule content in 3.5 minutes and insoluble material passed through the basket rack in 9.45 minutes to 11.10 minutes. Physical stability studies were carried out in different zones based on the different solubilizers used in the formulation process. Gelucire and Cremophore formulations showed good physical stability for up to three months, even at 40°C/75% RH, while PVP K-30 formulation exhibited capsule shell deformation within one month at 40°C/75% RH.

Weight variation test

To determine the uniformity of content and weight fluctuations in the final formulation, a weight variation test was conducted. This method involved recording the capsule size, the weight of the content to be filled into the empty capsule shells, and the average weight of the empty capsule shell. Three sets of ten capsules were used for all calculations. The actual filled weight was weighed, and the average weight of the band seal and the average weight after band sealing were determined. The average weight for three sets of ten capsules was calculated and presented in Table 2.

Dissolution time

The dissolution study was conducted using a Type II (paddle) disintegration apparatus with a volume of 900 ml and a controlled temperature of 37±20C using phosphate buffer 6.8[12]. The percentage release of PVP K-30 was highest, reaching 80% within 5 minutes and 107% in 30 minutes. However, stability studies revealed capsule shell deformation within 1 month at 400C/75% RH (Zone II). Among the Gelucire and Cremophore EL formulations, the Gelucire formulation showed promising results with 53% release at the 5-minute time point and up to 103% at 45 minutes. On the other hand, the Cremophore EL formulation showed a release of 36% at the 5-minute time point and up to 101% at the 30-minute time point. Additionally, both Gelucire and Cremophore EL formulations showed promising results based on their stability tests[13]. Figure 4 shows the drug release profile of Gelucire-based Diclofenac potassium-filled capsules showed a slower release rate than PVP K-30 but faster than Cremophore EL-based capsules in the first 5 minutes, as depicted in Figure 3. The Gelucire-based formulation released about 103% of the drug in 45 minutes, while the Cremophore EL-based formulation released only 36% in the first 5 minutes and 101% in 30 minutes. However, the PVP K-30-based formulation exhibited the highest percentage release, with 80% in the first 5 minutes and 107% in 30 minutes, but failed the stability study required for ideal results[14].

Partition Coefficient

The partition coefficient is a measure of the difference in solubility of compounds or formulations in two immiscible phases at equilibrium. This ratio is obtained by dividing the concentrations of the compound in each phase. One of the phases is typically hydrophilic, such as water, while the other is hydrophobic, such as octanol. The partition coefficient indicates the hydrophilicity or hydrophobicity of a compound based on its distribution in the respective phase due to its affinity. It is also known as the distribution coefficient[15]. In this study, the partition coefficient was determined using the flask method for formulations with different solubilizers, namely Gelucire, Cremophore EL, and PVP K-30. Table 4 shows that the Gelucire-

based formulation had a partition coefficient of 89% in the water portion (KO/W), while the Cremophore EL-based formulation had a partition coefficient of 68%. The PVP K-30-based formulation had a partition coefficient of 64%, which was the lowest among the three formulations.

The discussion revolves around the use of Diclofenac potassium as an anti-inflammatory drug and the need for new approaches to enhance its efficacy in relieving pain. The article suggests that developing a liquid capsule as an immediate release formulation could be a solution to this problem. The liquid capsule could provide faster and more effective concentrations of diclofenac, leading to a lower and more prolonged excruciating effect. The article provides a detailed description of the materials and methods used to create the liquid capsule, including the pH adjustment and the use of different solubilizers for different formulations.

The physicochemical properties of the liquid-filled capsules were examined, including clarity/turbidity of the solution, weight variation, leakage test after band sealing, density, and viscosity of the solution, disintegration test, and dissolution test. The disintegration test was conducted to confirm that the dosage form disintegrated within the expected time frame. The formulation was placed in a basket apparatus with a buffer system, and the drug release and absence of capsule or band material residue were evaluated. The disintegration test showed that the capsules cleared the capsule content in 3.5 minutes and insoluble material passed through the basket rack in 9.45 minutes to 11.10 minutes. Physical stability studies were carried out in different zones based on the different solubilizers used in the formulation process. Gelucire and Cremophore formulations showed good physical stability for up to three months, even at 40°C/75% RH, while PVP K-30 formulation exhibited capsule shell deformation within one month at 40°C/75% RH.

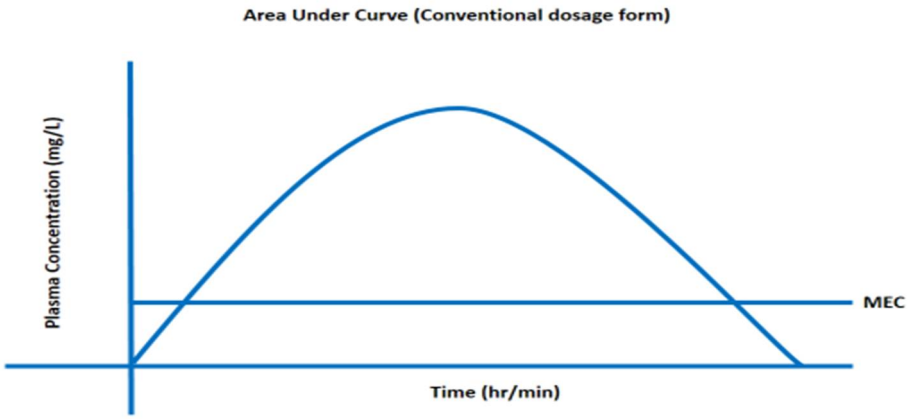


Figure 1: Area Under Curve (AUC) for conventional dosage form

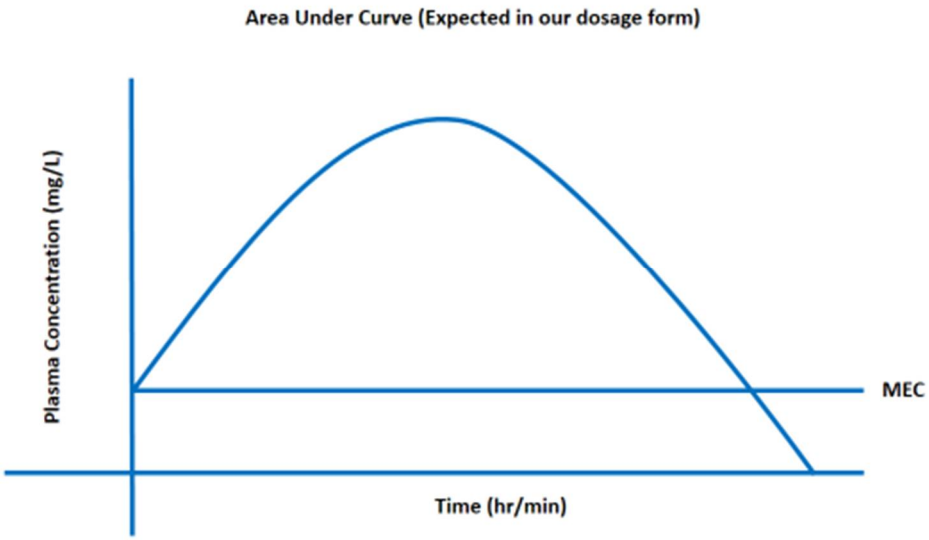


Figure 2: area under the curve (AUC) expected for our formulation

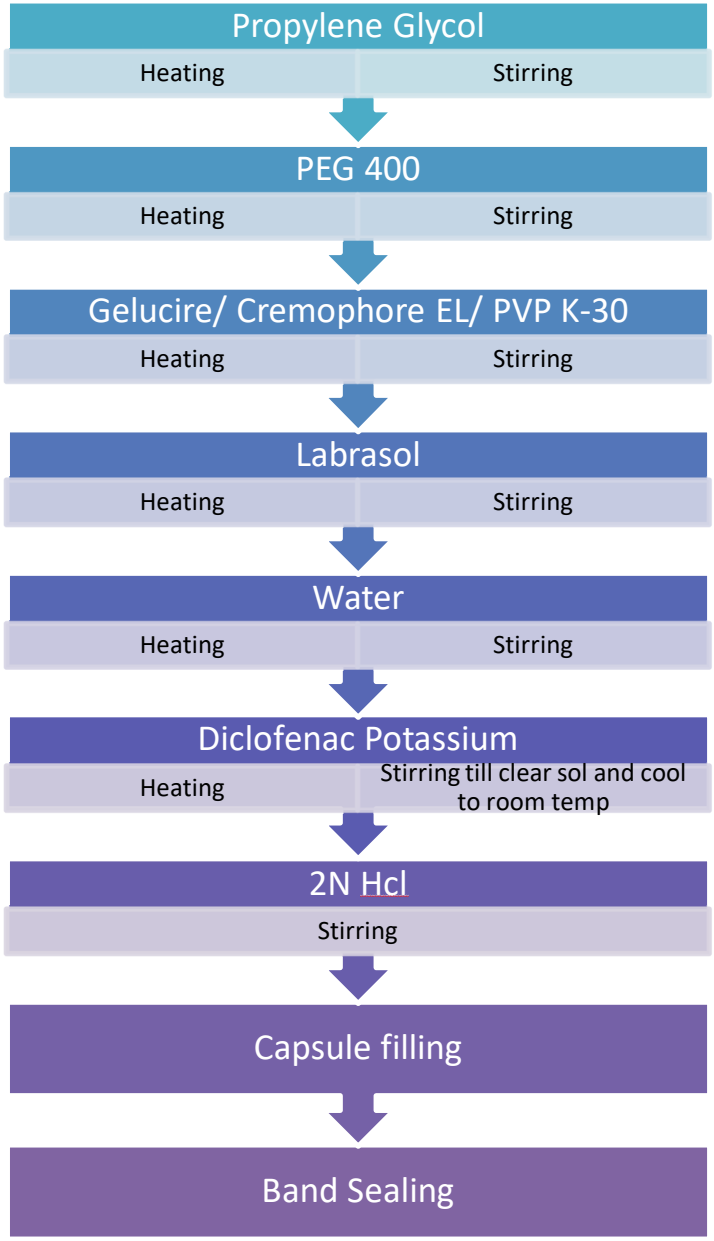
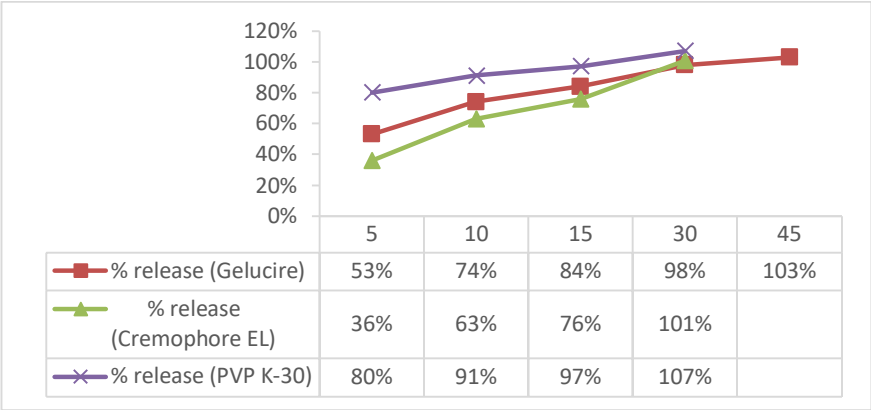


Figure 3: Flowchart for manufacturing of formulation



	5	10	15	30	45
% release (Gelucire)	53%	74%	84%	98%	103%
% release (Cremophore EL)	36%	63%	76%	101%	
% release (PVP K-30)	80%	91%	97%	107%	

Figure 4: Dissolution rate for formulations with Gelucire, Cremophore EL and PVP K-30

Table 1: Different strategies are followed for liquid manufacturing

Sr. No.	Ingredients	mg/Cap (Gelucire)	mg/Cap (Cremophore)	mg/Cap (PVP K-30)
1	Diclofenac Potassium	25.00	25.00	25.00
2	Propylene Glycol (PG)	21.60	21.60	40.00
3	PEG 400	21.60	21.60	40.00
4	Water	5.80	5.80	40.00
5	Labrasol	70.00	35.00	70.00
6	Gelucire 44/14	60.00	NA	NA
7	Cremophore EL	NA	90.00	NA
8	PVP K-30	NA	NA	5.00
	Total	**204**	**199**	**220.00**

Table 2: Weight variation test for 3 capsule sets

Sr. No.	Weight -filling test for capsule:	Capsule size '1'
1.	Weight fill (average weight mg)	226.37 mg to 229.32 mg
2.	Empty capsule shell weight (mg)	76.55
3.	Average weight (mg)	76.18; 76.84; 77.08
4.	Actual filled weight (mg)	226.37+76.84 = 303.21 & 229.32+77.08 = 306.40
5.	Weight before band sealing (mg)	303 to 307
6.	Average weight after band sealing (mg)	318.40
7.	Final Average weight of each set for 10 capsules (mg)	318.26; 319.17; 307.94

Table 3: Dissolution rate for formulations with different solubilzers

Time (mins)	% release (Gelucire)	% release (Cremophore EL)	% release (PVP K-30)
5	53	36	80
10	74	63	91
15	84	76	97
30	98	101	107
45	103	NA	NA

Table 4: Partition Coefficient: Determination of partition coefficient of samples in water and octanol.

Sr. No.	Batch formulations	Partition coefficient measurement in Octanol & water KO/W (% drug released)
1	Formulation with Gelucire	89%
2	Formulation with Cremophore EL	68%
3	Formulation with PVP K-30	64%

CONCLUSION

The present study investigates the impact of different solubilizers on liquid formulations for capsule filling. Various physicochemical parameters were assessed, including the manufacturing process, final solution clarity, release rate, and weight variation. Additionally, the solubilizers were evaluated for their effect on stability, dissolution rate, and partition coefficient. The in-vitro dissolution apparatus was used to conduct the study, and all three solubilizers, Gelucire 44/14, Cremophore EL, and PVP K-30, demonstrated immediate release within a 5-minute time span. The formulations with Gelucire 44/14 and Cremophore EL proved to be stable after 3 months, while the PVP K-30 formulation showed instability after one month, causing capsule deformation at 400C/75% RH. Partition coefficient studies favored all three formulations, with the dissolution coefficient rate being significant. The partition coefficient for Gelucire, Cremphore EL,

and PVP K-30 was found to be 89%, 68%, and 64%, respectively. The study showed that the desired effect was more prominent with Gelucire, Cremphore EL, and PVP K-30.

AUTHORS CONTRIBUTION

AQ and RF contributed to the development of the initial concept of the study and was responsible for the design and implementation of the methodology. RP and SH conducted the investigation, collected and curated the data, and wrote the original draft of the manuscript. DN and AQ was responsible for reviewing and editing the manuscript, creating visualizations, and supervising the overall progress of the study. All authors have read and approved the final manuscript.

Ethical approval and consent to participate

Not Applicable

Consent for Publication

Not Applicable

Availability of data and material

Not Applicable

Competing interests.

The authors declare no conflict of interest

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