IJPSR (2023), Volume 14, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 October 2022; received in revised form, 18 December 2022; accepted, 19 December 2022; published 01 January 2023

FORMULATION AND EVALUATION OF LIQUID-FILLED HARD GELATIN CAPSULE OF DICLOFENAC POTASSIUM

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Keywords:

Liquid filled hard gelatin capsule, Diclofenac potassium, analgesic, anti-inflammatory

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ABSTRACT: Background Diclofenac Potassium is the potassium salt form of diclofenac, a benzene acetic acid derivate, and nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory activity. **Aim:** Therefore, the purpose of the present study was to formulate and evaluate liquid-filled hard gelatin capsules of diclofenac potassium. **Methods:** The liquid-filled soft 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 was finally added to the mixture under stirring. The final formulation was filled in a hard gelatin capsule, and the hand band seal was performed. Physico-Chemical Evaluation**:** A total fifteen liquid-filled hard gelatin capsule formulations were prepared (F-1 to F-15) and evaluated for weight variation test, lock length, drug content, nephelometric turbidity units (NTU) and in-vitro release study. **Results:** The drug content ranged from 92.76±0.12 to 99.25 ±0.19. The results indicated that the drug content was uniform in all the formulations. The disintegration time ranges from 130 sec to 232 sec. *In-vitro* dissolution study shows % cumulative drug release ranging from 84.10±1.76 to 99.57±0.653. Optimized formulation F14 at 40± 2ºC, 75 ± 5% RH was found to be stable up to 30 days. **Conclusion**: Hence liquid filled hard gelatin capsule of diclofenac potassium can be a potential alternative to available traditional oral drug delivery systems of diclofenac potassium to improve its bioavailability.

INTRODUCTION: Capsules were used because it was simple to formulate them as unit dosage forms for drugs formulated to liquid form and because they provided an easy-to-swallow container that effectively masked the bitter taste of drugs [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(1).512-18

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(1).512-18

With the advent of pellet or liquid-filled technology that enabled modified drug release, capsules provided a useful vehicle into which micronized form could be filled without the risk of modifying the release characteristics associated with other processing methods, such as compression of multiparticulates into tablets.

Here we can study the effect of enhancing the bioavailability of a dosage form that has been changed to liquid from a solid formulation filled in the empty hard gelatin capsule shell. Since, the early 1980s, technology has been available to

permit accurate dosing and sealing of liquids into hard gelatin capsules [2, 3]. The empty capsule shells are made of gelatin, sugar, and water. As such, they can be clear, colorless and essentially tasteless; or they may be colored with various dyes and made opaque by adding agents such as titanium dioxide [4]. Most commercially available medicated capsules contain combinations of colorants and opaquants to make them distinctive, many with caps and bodies of different colors. Gelatin is obtained by the partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals [4]. In commerce, it is available in the form of fine powder, a coarse powder, shreds, flakes, or sheets. Gelatin is soluble in hot water and in warm gastric fluid; a gelatin capsule rapidly dissolves and exposes its contents. Gelatin, being a protein, is digested by proteolytic enzymes and absorbed [5, 6]. Diclofenac Potassium inhibits prostaglandin synthesis by interfering with the action of prostaglandin synthetase, which explains its action. It is ideally suited for patients on a sodium-free diet, hypertensive patients, to treat painful inflammatory conditions of patients such as arthritis. Diclofenac potassium is soluble in water and rapidly absorbed from GIT [7, 8].

MATERIALS AND METHOD: Diclofenac sodium was borrowed from Wockhardt Ltd., Aurangabad. Polyvinyl pyrrolidone was purchased from Moly chem, Mumbai. Polyethylene glycol (PEG) was purchased from Loba Chemie, 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.

Preparation of Liquid Filled Hard Gelatin Capsule:

Preparation of Liquid Formulation F14 to be filled in Hard Gelatin Capsule [13, 16, 39, 42]:

Method: To a container PEG 400 (10%), propylene glycol (10%) and water (3%) were added under stirring and heating. The product temperature was maintained at 90°C. To the above step, slowly PVA (4%) was added under stirring and product temperature was maintained at 90ºC.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 90ºC. The final formulation was filled in a hard gelatin capsule, and a hand band seal was performed [9, 10].

TABLE 1: COMPOSITION OF LIQUID FILLED IN HARD GELATIN CAPSULE

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

Evaluation Parameters of Liquid-Filled Capsules:

Weight Variation Test: All the filled capsules were subjected for a weight uniformity test. Here, each individual capsule was calculated by adding up its weight for empty capsule shell weight in mg, liquid weight to be filled in a hard gelatin capsule and band seal weight.

In this test 20 units of capsules were weighed individually and the average weight was calculated from which percentage deviation was determined [11].

Lock Length: Lock length is the size of the capsule shell from one end to the locking area of cap and body of the capsule shell. Lock length can be used to determine the capsule size, empty capsule weight and filling capacity by using the formula M=V x D (M = Mass, V = Volume and D = Density of contents). The capsule lock lengths for individual formulations were measured using vernier caliper [12].

Drug Content: The drug content was carried out in triplicate for all the formulations. Accurately weighed capsules containing equivalent to 25 mg of diclofenac potassium were suspended in methanol using 100 ml volumetric flask.

The solution was kept aside for 48 hours. After 48 hours, the solution is stirred for 5 minutes and filtered. Filtrate was suitably diluted to achieve a concentration of 0.75 mcg/ml and was analyzed at 282 nm using UV-1800 series spectrophotometer instrument against methanol as blank [13].

***In-vitro* Release Study:** The *in-vitro* release of the drug from liquid-filled hard gelatin capsules was carried out for 45 minutes using dissolution apparatus USP type II. Liquid-filled in hard gelatin capsules consists of a drug equivalent to 25 mg.

We studied the release for every 15 minutes in 6.8 phosphate buffer was used and was replaced with same pH 6.8 phosphate buffer for every 15 minutes till 45 minutes of release. The dissolution media was maintained at 37ºC±0.5ºC and a speed of 50 rpm. At prefixed time intervals (every 15 minutes), 5 ml of solution was withdrawn and replaced with 5 ml of fresh buffer solution.

After suitable dilutions, the samples were analyzed at 282 nm with phosphate buffer using UV-1800 series spectrophotometer [14].

Statistical Analysis: Statistics is a logic, which makes use of mathematics in the science of collecting, analyzing and interpreting data for the purpose of making decisions.

Now, after many evaluations carried out on all the formulations of liquid filled in hard gelatin capsules the data obtained were subjected to statistical analysis of formula F_{14}. A computer aided calculations were done by using a preprogrammed software [15].

Nephelometric Turbidity Units (NTU): NTU are based on white light (400–680nm) and 90° incident angle. Many liquids are essential in our daily lives, such as water, chemicals, acids, bases or pharmaceutical products such as our samples. The quality of these liquids is determined by their chemical and physical properties. To asses these properties various principles of measurement are used as in case of our research study. One of these principles is measurement of turbidity in liquid. Turbidity is the cloudiness caused by suspended particles of liquid.

These particles scatter the incident light, and the liquid loses its transparency. The instrument used was a digital nephelometer; it has a holder for a glass tube with lid to cover, where we start by keeping the standard samples for calibration. Another segment is for power, where we run the experiment by switching the mode towards the on the segment.

The calibration is performed using our standard sample/s, that is distilled water so instrument is calibrated. Then we use our samples for analysis to measure the turbidity and the turbidity of our sample/s is measured as shown on nephelometer in NTU.[16]

Correlations: The coefficient of correlation (r) was calculated with the help of computer-aided preprogrammed software. The ‘t’ values fo ‘t-test of significance were also calculated. Considering the linear correlation y=bx+a, the b value (slope) and a value (y-intercept) were obtained [17].

Model Fitting for Release of Diclofenac Potassium from Liquid-Filled Hard Gelatin Capsule:

The different drug release profiles were calculated and analyzed for best fit models by incorporating the data into:

1. Zero Order
2. First Order
3. Higuchi
4. Korsmeyer Peppas

RESULT AND DISCUSSION:

S. no.	Conc ppm	Absorbance in Methanol	Absorbance in pH 6.8
1	21	0.872	0.164
2	14	0.581	0.108
3	7	0.300	0.054
4	3.5	0.141	0.024
5	1.4	0.118	0.026
6	0.7	0.03	0.008
7	0.14	0.016	0.005

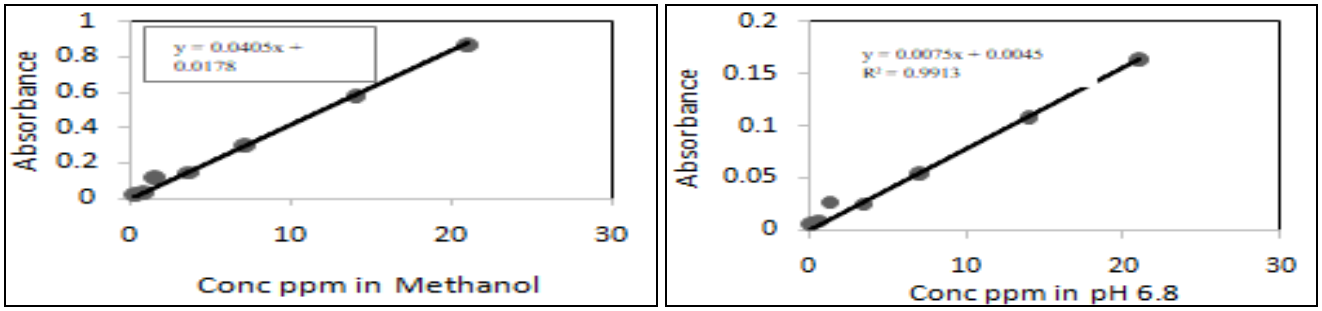

FIG. 1: STANDARD CALIBRATION CURVE OF DICLOFENAC POTASSIUM IN PH 6.8 PHOSPHATE BUFFER (λMAX=282 NM)

TABLE 1: PHYSICOCHEMICAL PARAMETERS OF LIQUID FILLED HARD GELATIN CAPSULES

Formulation Code	Parameters		
	Lock length Avg (mm)	Disintegration time (sec)	Drug content (%)
F1	17.19+0.07 mm	210	92.76±0.12
F2	17.19+0.07 mm	230	94.51±0.24
F3	15.35+0.04 mm	232	97.50±0.28
F4	17.19+0.07 mm	180	95.01±0.09
F5	15.35+0.04 mm	150	97.25±0.14
F6	17.19+0.07 mm	172	96.50±0.06
F7	15.35+0.04 mm	160	95.76±0.38
F8	17.19+0.07 mm	170	98.76±0.12
F9	17.19+0.07 mm	158	97.28±0.35
F10	17.19+0.07 mm	168	95.51±0.47
F11	17.19+0.07 mm	148	98.25±0.56
F12	18.84+0.08 mm	130	96.75±0.31
F13	18.84+0.08 mm	135	98.08±0.38
F14	17.19+0.07 mm	210	96.75±0.04
F15	17.19+0.07 mm	224	99.25±0.19

TABLE 2: DISSOLUTION PROFILE OF DICLOFENAC POTASSIUM FROM FORMULATION F1-F15

Formulations	Time point		
	15 min	30 min	45 min
F1	78	88	89
F2	65	73	81
F3	81	90	93
F4	75	88	98
F5	98	99	99
F6	72	78	83

F7	79	84	86
F8	89	91	91
F9	88	92	97
F10	89	90	84
F11	98	93	96
F12	102	97	98
F13	88	91	97
F14	94	97	99
F15	75	88	98

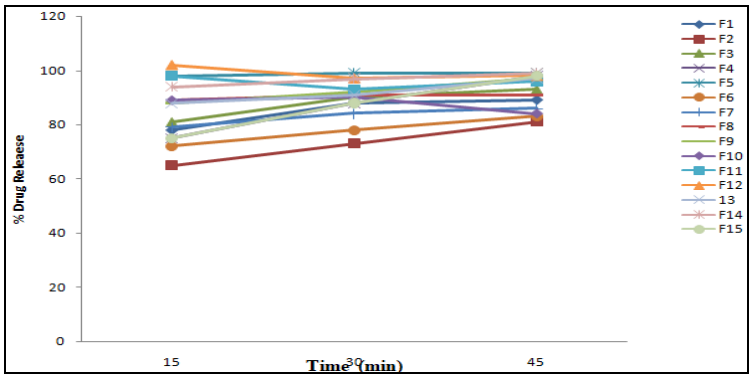

FIG. 2: % DRUG RELEASE OF LIQUID-FILLED HARD GELATIN CAPSULES (F1-F15)

TABLE 3: *IN-VITRO* DRUG RELEASE FROM FORMULATION

Time (min)	Cumulative % drug released	% Drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% drug released	Cube Root of % drug Remaining (Wt)
0	0	100	0.000	2.000	0.000	0.000	100	4.642
15	94.00	6	3.873	0.778	1.176	1.973	94	1.817
30	99.00	1	5.477	0.000	1.477	1.996	5	1.000
45	99.00	1	6.708	0.000	1.653	1.996	0	1.000

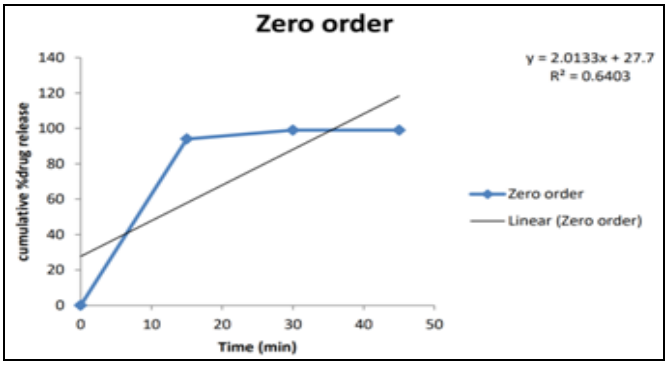

FIG. 3: ZERO ORDER PLOTS OF LIQUID FILLED HARD GELATIN CAPSULE (F14)

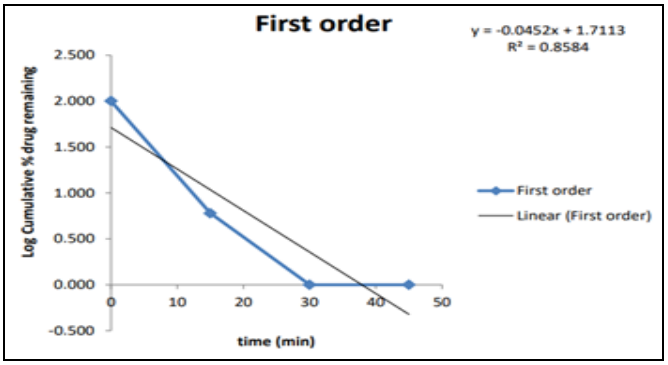

FIG. 4: FIRST-ORDER PLOTS OF LIQUID FILLED HARD GELATIN CAPSULE (F14)

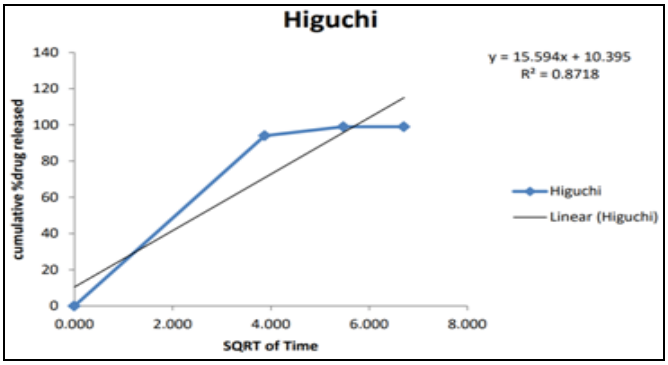

FIG. 5: HIGUCHI'S DISSOLUTION PLOTS FOR LIQUID-FILLED HARD GELATIN (F14)

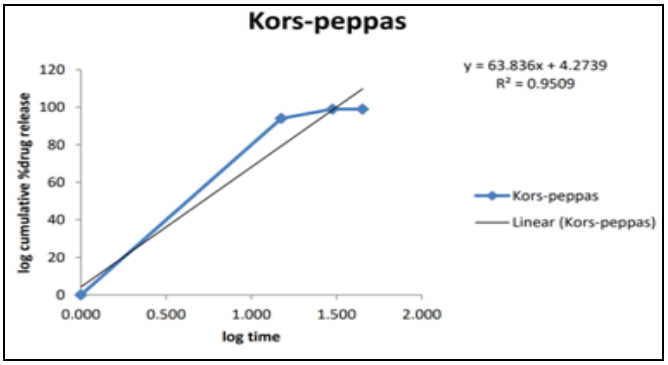

FIG. 6: KORSMEYER-PEPPAS DISSOLUTION PLOTS FOR LIQUID-FILLED HARD GELATIN (F14)

TABLE 4: NEPHELOMETRIC TURBIDITY UNITS (NTU)

S. no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
formula	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
NTU (min to max)	635 to 757	692 to 785	221 to 310	710 to 884	593 to 661	584 to 637	546 to 607	511 to 623	587 to 603	446 to 477	881 to 921	563 to 761	283 to 249	148 to 157	187 to 193

NTU are based on white light (400–680nm) and 90° incident angle.

The weight of each liquid-filled capsule was taken on Electronic analytical balance, and the weight variation was calculated as mean SD. The drug content of optimized batches was calculated using liquid filled capsule containing diclofenac potassium. Three trials from each formulation are analyzed spectrophotometrically. The mean value and standard deviation of all the formulations are calculated. The drug content ranged from 92.76±0.12 to 99.25 ±0.19. The results indicated that in all the formulations, the drug content is uniform.

The capsules were placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37ºC. To fully satisfy the test, the capsules should disintegrate completely into a soft mass having no palpably firm core without any fragments of the gelatin shell. The disintegration time ranges from 130 sec to 232 sec. The result indicated that all the formulations show less deviation in the disintegration profile, possibly because of the same size & type of capsule shell used. The release of the drug was determined using a dissolution apparatus of USP type II paddle at 50 rpm at 900 ml of volume, and 0.1 N HCl solution was used as a dissolution media and maintained at temp 37.5ºC for 60 min. In-vitro dissolution study shows % cumulative drug release ranging from 84.10±1.76 to 99.57±0.653.

To analyze the mechanism of drug release of the optimized batch (F14) of the liquid-filled hard gelatin capsule was obtained from the drug release studies, which were subjected to mathematical model of korsemeyer' peppers. The correlation coefficient (r^2) was used as an indicator for the best fitting for each of the models. The drug release mechanism of a liquid-filled hard gelatin capsule of diclofenac potassium is shown above. Optimized formulation F14 at 40±2ºC, 75 ± 5% RH was found to be stable up to 30 days. There was no significant change in drug content visual appearance *i.e.*, changes in color. All Formulations stored at elevated temperatures showed very slight changes in disintegration time, drug content, and drug release.

CONCLUSION: Liquid filled hard gelatin capsule of diclofenac potassium was prepared using different solubilizing agents. The drug content & drug release was found to be maximum in the capsule (F14). From the obtained data of our experimentation, liquid filled hard gelatin capsule of diclofenac potassium can be a good alternative to conventional uncoated marketed formulation with possible improvements in the absorption of the drug & subsequent bioavailability.

ACKNOWLEDGEMENT: NIL

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

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How to cite this article:
Quazi A and Hafiz RF: Formulation and evaluation of liquid filled hard gelatin capsule of diclofenac potassium. Int J Pharm Sci & Res 2023; 14(1): 512-18. doi: 10.13040/IJPSR.0975-8232.14(1).512-18.