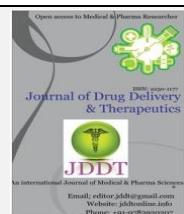


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Research Article

Formulation and Evaluation of Liquid Filled Hard Gelatin Capsule of Febuxostat

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ABSTRACT

Liquid filled hard gelatin capsule are well recognized as a solid dosage form for convenient administration of drugs orally in a liquid form. This liquid composition available help the most challenging drug compounds in capsules has increased significantly in recent years. The drugs which have low solubility, poor bioavailability, low melting point, critical stability are the perfect candidate for liquid filling in capsule. The current study presents the formulation aspects, filling and sealing aspects of capsule, evaluation parameters of the liquid filled hard gelatin capsule using Febuxostat as drug, oils (Arachis oil, Coconut oil, Olive oil) as solvents, Glyceryl monostearate as solubilizing agent, Butylated hydroxy toluene as antioxidant, Methyl paraben & Propyl paraben as preservatives. A capsule formed F3 formulation shows maximum drug release and drug content among all the formulations.

Keywords: Liquid filled hard gelatin capsule, Febuxostat, Arachis oil, Coconut oil, Olive oil, Glyceryl monostearate, Butylated hydroxy toluene, Methyl paraben, Propyl paraben.

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INTRODUCTION

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. 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. 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. 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.¹

Febuxostat is a novel drug which is developed for the treatment of gout and hyperuricemia. As an inhibitor of xanthine oxidase, it provides a selective and potent property compared with allopurinol.² FXT acquired admission from the Food and Drug Administration (FDA) in 2009. It was the first new drug the FDA approved in 40 years, which was used for lowering the level of serum uric acid in vivo.³ In recent years FXT has acquired extensive attractions owing to its good therapeutic effect. FXT is a weak acid (PKa 3.42)⁴ which is practically insoluble in water and the solubility was about 12.9 µg/ml in water at 37 °C.⁵ The bioavailability of FXT is approximately 80% and the half-life is about 5–8 hrs.⁶ FXT is classified as a Biopharmaceutics Classification System (BCS) II drug due to its low solubility and high permeability.⁷ In general, the primary problem of formulation for BCS II drugs is how to improve the dissolution. Water solubility is the main factor that influences the bioavailability of this kind of drug.⁸ Although FXT shows good pharmaceutical behavior, the improvement of aqueous solubility would be conducive to the absorption process.⁹ Poor aqueous solubility could be

improved in many ways, such as nanosuspension, solid dispersion, co-crystals, hydrates and salts, liquid formulations using oil as solvent.¹⁰⁻¹² The purpose of the present study was to provide a novel way to improve the aqueous solubility and in vivo bioavailability of FXT.

Drug categories suitable for Liquid filled capsules

1. Drugs with Poor bioavailability:

The bioavailability of the poorly water-soluble drugs can be significantly enhanced when formulated as a liquid in a hard gelatin capsule.^{13,14}

2. Drugs with Low melting point:

Materials having low melting points or are liquid at room temperature have some problems when formulating as dry powders, often requiring high concentrations of excipient to avoid processing problems.¹⁵

3. Potent drugs:

Drugs in this category present two main challenges; content uniformity and cross-contamination and worker protection.^{16,17}

4. Sustained release drug candidates:

By choosing an appropriate excipient the release rate of an active ingredient can be modified. E.g., soybean oil and glyceryl monostearate.¹⁸

The objective of study was to prepare Liquid filled hard gelatin capsule of Febuxostat which can be useful in Gout therapy. Liquid filled hard gelatin capsule prepared by simple mixing oils (Arachis oil, Coconut oil, Olive oil), Glyceryl monostearate, Butylated hydroxy toluene, Methyl paraben & Propyl paraben as preservatives and filled into capsule of size 00. It was sealed by banding technique using 15% w/v gelatin solution. The prepared capsules were evaluated for weight variation, content uniformity, disintegration, dissolution studies, release kinetics and

stability studies. The formulation was compared with marketed formulation of Febuxostat (Febucip 40).

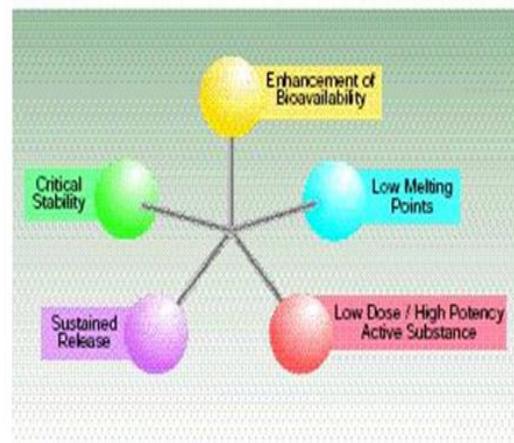


Figure 1. Reasons for Formulating Drugs as Liquid Dosage

MATERIALS & METHODS

Febuxostat as a gift sample from Ami Lifesciences, Vadodara, Arachis oil from Modern industries, Sinnar, Olive oil from Evonik, Kolkata, Coconut oil, GMS from LOBA CHEMIE PVT LTD, Mumbai, BHT, Methyl & Propyl paraben from Research lab fine chem industries, Mumbai.

Preparation of Liquid filled hard gelatin capsule

Weigh Febuxostat 40mg and dissolved in 1ml Arachis, Coconut & Olive oil. Add GMS, BHT, Methyl & Propyl paraben. Prepared formulation was filled into capsule size 00. The capsule was sealed by banding technique using 15% w/v gelatin solution.

Table 1. Composition of Febuxostat Liquid filled Hard gelatin Capsule

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Febuxostat (mg)	40	40	40	40	40	40	40	40	40
Arachis Oil (ml)	1	1	1	-	-	-	-	-	-
Coconut Oil (ml)	-	-	-	1	1	1	-	-	-
Olive Oil (ml)	-	-	-	-	-	-	1	1	1
GMS (mg)	10	15	20	10	15	20	10	15	20
BHT (mg)	1	1	1	1	1	1	1	1	1
Methyl:Propyl Paraben (mg)	0.2 (1:1)	0.2 (1:1)	0.2 (1:1)	0.2 (1:1)	0.2 (1:1)	0.2 (1:1)	0.2 (1:1)	0.2 (1:1)	0.2 (1:1)

Evaluation parameters of liquid filled capsules

1. Weight variation test

Fill the capsule shell with formulation. Take 20 capsules and weight of individual capsule should be noted and average weight is calculated. Not more than two individual weight deviates from average weight.⁽¹⁵⁾

2. Content uniformity:

Intact capsule was weighed. The capsule was opened without losing any part of the shell and contents were removed as completely as possible. The shell was washed with ether or other suitable solvent and the shell allowed to stand until the odour of the solvent was no longer detectable. By using UV Spectroscopy content uniformity was calculated.

3. Disintegration:

The capsules were placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a

thermostatically controlled fluid at 37°C. 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. If one or two capsules fail the test should be repeated for additional of 12 capsules. Then not fewer than 16 of the total 18 capsules tested should disintegrate completely.

4. Dissolution studies:

Dissolution is a process by which the disintegrated solid solute converted into solution. The test determines the time required for a definite percentage of the drug in capsules to dissolve under specified conditions. The release of drug was determined using a dissolution apparatus of USP type II paddle at 50 rpm 900 ml of 0.1 N HCl solution was used as a dissolution media and maintained at temp 37.5°C for 60 min. The dissolution study of liquid filled hard gelatin capsule was compared with marketed formulation of Febuxostat (Febucip 40). The data was subjected for kinetic model. The kinetic modeling of drug release and the model with the higher correlation coefficient i.e. higher R^2 was considered to be the best fit model.

5. Stability studies:

Preliminary stability of the best formulation obtained by investigating its Physical characteristics and drug content and drug release after storage at stressed conditions. LFHGC was stored at $40\pm2^{\circ}\text{C}$ & $75\pm5\%$ RH for a period of 1 month. The Physical characteristics and drug content and drug release of the fresh (stored at room temperature) and stressed preparations are compared to evaluate the stability and effect of aging.

RESULT AND DISCUSSION

1. Weight variation

The weight of each liquid filled capsule was taken on Electronic analytical balance and the weight variation was calculated as mean SD. Weight variation varies from 98.60 ± 0.945 to 102.3 ± 2.210 .

2. Content uniformity:

Drug content of optimized batches were calculated by using liquid filled capsule containing 40 mg of febuxostat. Three trials from each formulation are analyzed spectrophotometrically. The mean value and standard deviation of all the formulations are calculated. The drug content ranging from 97.05 ± 2.155 to 99.31 ± 2.455 . The results indicated that in all the formulations the drug

content is uniform. The studies also show that uniformity of content is in the range of 85-115%.

3. Disintegration:

The capsules were placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37°C. 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. Limit of disintegration is 30 min. The disintegration time ranging from 33.0 ± 0.535 to 38.0 ± 1.1305 . The result indicated that all the formulations shows very less deviation in disintegration profile which may be because of the same size & type of capsule shell used.

4. Dissolution studies

The release of drug was determined using a dissolution apparatus of USP type II paddle at 50 rpm 900 ml of 0.1 N HCl solution was used as a dissolution media and maintained at temp 37.5°C for 60 min. In-vitro dissolution study shows % cumulative drug release ranging from 80.10 ± 0.80 to 98.57 ± 0.993 . Maximum release i.e. 98.57% for F3 formulation this could be attributed due to higher concentration of GMS in the formulation.

In vitro dissolution profile of liquid filled capsule (F3) and Marketed formulation (Febucip 40) are compared together. Liquid filled capsule of febuxostat shows more % drug release than the marketed formulation which may be because of undissolved amount of the drug present in marketed formulation even after 60 min.

5. Kinetics of drug release:

To analyze the mechanism of drug release of the optimized batch (F3) of the liquid filled hard gelatin capsule was obtained from the drug release studies which was subjected to mathematical model of korsemeyer's peppas. The correlation coefficient (r^2) was used as an indicator for the best fitting for each of the models. The table 7 shows the Kinetics treatment for the optimized formulation(F3). The drug release mechanism of liquid filled hard gelatin capsule of febuxostat was shown below.

6. Stability studies:

Optimized formulation F3 at $40\pm2^{\circ}\text{C}$, $75\pm5\%$ 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 temperature showed very slight changes in disintegration time and drug content and drug release.

Table 2. Evaluation of Febuxostat Liquid filled Hard gelatin Capsule

Sr.No.	Formulation code	Average weight (mg) Mean \pm SD	Drug content (%) Mean \pm SD	Disintegration time (min) Mean \pm S.D.
01	F1	98.70 \pm 0.807	97.10 \pm 2.160	36.7 \pm 1.141
02	F2	99.0 \pm 0.894	98.35 \pm 2.350	34.2 \pm 0.580
03	F3	98.60 \pm 0.945	99.31 \pm 2.455	33.0 \pm 0.535
04	F4	101.75 \pm 1.512	97.05 \pm 2.155	37.3 \pm 1.230
05	F5	100.5 \pm 1.554	98.20 \pm 2.310	35.0 \pm 0.860
06	F6	102.10 \pm 1.575	99.08 \pm 2.425	33.3 \pm 0.550
07	F7	101.0 \pm 2.120	97.40 \pm 2.425	38.0 \pm 1.1305
08	F8	102.3 \pm 2.210	98.71 \pm 2.390	35.5 \pm 0.875
09	F9	99.5 \pm 2.090	99.15 \pm 2.433	33.1 \pm 0.400

Table 3. Dissolution study of liquid filled hard gelatin capsule of Febuxostat

TIME IN MIN	% CUMULATIVE DRUG RELEASE ± S.D								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	52.80 ± 0.315	55.7 ± 0.401	61.5 ± 0.522	43.6 ± 0.478	59.8 ± 0.309	63.2 ± 0.510	41.0 ± 0.620	54.8 ± 0.711	50.6 ± 0.840
20	63.34 ± 0.300	69.94 ± 0.501	77.85 ± 0.650	55.95 ± 0.670	70.18 ± 0.550	75.10 ± 0.525	50.03 ± 0.740	65.51 ± 0.415	61.60 ± 0.190
30	71.43 ± 0.595	75.49 ± 0.550	84.21 ± 0.830	62.10 ± 0.250	77.28 ± 0.610	81.25 ± 0.826	56.54 ± 0.785	72.30 ± 0.540	68.50 ± 0.490
40	79.10 ± 0.670	85.51 ± 0.880	90.65 ± 0.940	70.48 ± 0.560	84.59 ± 0.855	89.69 ± 0.895	64.80 ± 0.343	78.90 ± 0.630	75.27 ± 0.534
50	84.72 ± 0.861	89.92 ± 0.900	94.85 ± 0.873	79.20 ± 0.685	90.04 ± 0.911	93.80 ± 0.965	73.59 ± 0.651	83.82 ± 0.775	85.10 ± 0.870
60	88.51 ± 0.795	95.17 ± 0.971	98.57 ± 0.993	84.38 ± 0.842	94.49 ± 0.964	96.35 ± 0.984	80.10 ± 0.805	89.14 ± 0.890	91.85 ± 0.924

Table 4: In vitro dissolution profile of liquid filled capsule (F3) and Marketed formulation (Febucip 40)

Sr.no.	Time (min)	% Drug Release	
		Liquid filled capsule (F3)	Marketed formulation (Febucip 40)
1	10	61.53	28.524
2	20	77.85	35.690
3	30	84.21	46.327
4	40	90.65	59.016
5	50	94.85	68.128
6	60	98.57	70.269

Table 5. R² values for Korsemeyer's peppas release kinetics

Formulation Code	F3
R ² value	0.985

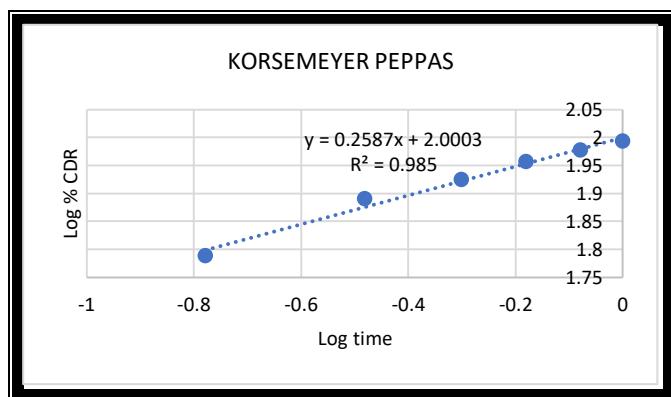


Table 6. Stability data for F3 formulation

SR. NO	OBSERVATION	BEST STABILITY TESTING	AFTER STABILITY TESTING
1.	Visual appearance (Color changes)	No change	No change
2.	Drug content	99.31%	99.28%
3.	Disintegration time	33 min	34 min
4	Drug release	98.57%	98.45%

CONCLUSION

Liquid filled hard gelatin capsule of Febuxostat was prepared using different oils. The drug content & drug release was found to be maximum in the capsule containing Arachis oil & maximum concentration of Glyceryl monostearate (F3). From the obtained data of our experimentation, liquid filled hard gelatin capsule of Febuxostat can be a good alternative to conventional uncoated marketed formulation with possible improvements in the absorption of the drug & subsequent bioavailability.

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