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Formulation and evaluation of flurbiprofen aqueous injection

Abstract

Objective: The objective of this research was to formulation and evaluation of flurbiprofen aqueous injection.

Methods: The flurbiprofen aqueous injection was successfully developed by mixed hydrotrophy technique, using sodium benzoate, sodium acetate, and propylene glycol, glycerin, peg200, peg400, peg4000, peg6000, urea and ethanol as solvent in various proportions in combination. Further, the prepared aqueous injection were characterized for qualitative solubility, quantitative solubility, dilution study, effect of ph extractable volume test, viscosity, visual check, bet test, sterility test, particulate contamination, compatibility studies (FTIR) and stability studies.

Results: The consequences of solvency studies are exhibited. It appears from the outcomes that the watery dissolvability of flurbiprofen was expanded more circumstances in hydrotropic mix specialists (PG25%+PEG10%+S5%), (SB5%+PEG 25%+S10%).1 In hydrotropic arrangement which additionally utilized for group assembling and testing reason all cluster demonstrates great soundness and manufactured products show stable results.

Conclusion: The dissolvability assurance of flurbiprofen was completed in distilled water, hydrotropic arrangements containing diverse convergences of hydrotropic. It is possible to make further more studies to develop for industrial manufacturings.

Keywords: flurbiprofen, hydrotropic, aqueous injection

Volume 1 Issue 2 - 2017

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Received: August 28, 2017 | **Published:** September 05, 2017

Introduction

Flurbiprofen is used to treating rheumatoid arthritis or osteoarthritis andanklosing spondylitis. It is BCS class II drug (low soluble & high permeable).[2] It is basically available as tablet form solubility was carried out using various co-sovents and hydrotrops. It may also be used for other conditions as determined by doctor. Flurbiprofen is an NSAID. Flurbiprofen are indicated for the acute or long-term symptomatic treatment of rheumatoid arthritis, osteoarthritis and anklosing spondylitis. After conducting patent search & literature survey on formulations containing drugs of certain class such as nonsteroidal anti-inflammatory drugs, development of flurbiprofen injection using mixed solvency and hydrotropic method not patented. Based on literature review & marketed products, it was concluded that there is opportunity for working in area of development of injection containing flurbiprofen for rheumatoid arthritis or osteoarthritis.[3]

Materials

The drug provide by montage labs. pvt ltd, himatnagar. Excipients used as LR grades.

Prefomulation study

Standard curve of flurbiprofen in methanol: the standard curve of flurbiprofen was prepared in methanol as shown in Figure 1 & Table 1.

Solubility trials in different solvents and ph solutions

All the sample of saturated solution of drug at different pH were shaken in an orbital shaker for 6 hours at 25°C and 60 RPM[4,5] and further equilibrated for next 48 hr after centrifugation and filtration the absorbances were recorded at 247 nm suing respective solution as blank.

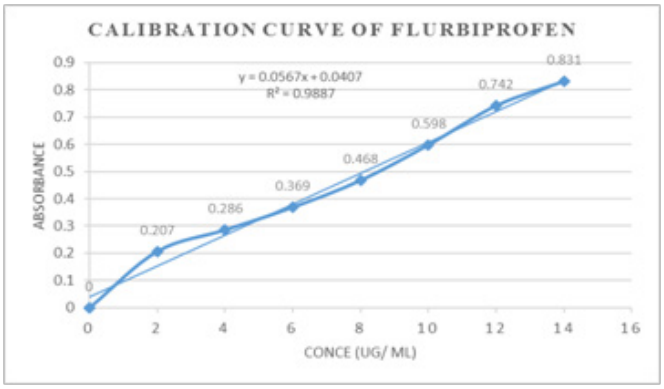

Figure 1 Flurbiprofen Curve.

Table 1 Standard curve

S. No.	Conc (mg/ml)	Absorbance
1	0	0
2	2	0.207
3	4	0.286
4	6	0.369
5	8	0.468
6	10	0.598
7	12	0.742
8	14	0.831

Procedure for 20% and 40% concentrations

Solubility of flurbiprofen invarious solution was determined by shack flask method. Excess amount of drug was added to 10ml Stoppard volumetric flask. Various hydrotropes in 20% and 40% Concentration solution in distilled water were filled in the volumetric flask. The flask was shaken for 6 hr in orbital shaker at 25°C and 60 RPM speed. The solution was allowed to equilibrate for the next 24hr. The solutions were then centrifuged for 10min at 1000rpm. Supernatant of each sample were filtered through 0.45 membrane filter and analyzed for drug content spectrophotometrically at 247nm after suitable dilutions.[6]

Procedure for 5 %, 25% and 10% concentrations

Solubility of flurbiprofen in various solutions was determined by Shak flask method. Excess amount of drug was added to 10ml stoppered volumetric flask. Various hydrotropes in 5%, 25% and 10% concentration solution in distilled water were filled in the volumetric flask. The flask was shaken for 6 hr in orbital shaker at 250°C and 60rpm speed. The solution was allowed to equilibrate for the next 24hr. The solution was then centrifuged for 10min at 1000rpm. Supernatant of each sample were filtered through 0.45 membrane filter and analyzed for drug content spectrophotometrically at 247nm after suitable dilutions (Table 2) (Table 3).[7]

Table 2 Analyzed for drug content spectrophotometrically at 247 nm after suitable dilutions

S. No	Sample	20 % Conc		40 % Conc	
		Conc (mg/ml)	Sol. in Fold	Conc (mg/ml)	Sol. in Fold
1	Dist. water	0.03	1	0.03	1
2	PG	1.56	52	31.4	1046
3	PEG 200	0.685	22	28	933
4	PEG400	1.265	42	54	1800
5	Ethanol (95%)	7.412	247	95	3166
6	Methanol	8.365	278	97	3233
7	Chloroform	0.995	33	86	2866
8	Glycerin	0.484	16	31.23	1041
9	HCL 1.2	0.142	4	8.36	278
10	Phos BFR 4	0.262	8	15.36	512
11	Phos BFR 6.8	4.23	141	26	866
12	Phos BFR 7.4	6.201	206	55	1833
13	Sod. Acetate	0.734	24	43.56	1452
14	Sod. Benzoate	0.785	26	56.39	1879
15	PEG-6000	0.712	23	62.36	2078
16	PEG-4000	0.655	21	53.26	1775
17	UREA	0.856	28	67.34	2244

Table 3 Solubility in different hydrotrops

Sample	Conc mg/ml	Conc mg/ml	S. in fold	
1	PG 5 % +PEG 10%+S 25 %	64.78	2159	
2	PG 5 % +PEG 25%+S 10%	78.34	2611	
3	PG 25 % +PEG 10%+S 5 %	124.56	4152	F1
4	PG 25 % +PEG 5 %+S 10%	105.45	3515	
5	PG 10 % +PEG 25 %+S 5%	87.56	2918	
6	PG 10 % +PEG 5 %+S 25%	74.789	2492	
7	15%PG +25% S	168.78	5626	
8	SB 5 % +PEG 10%+S 25 %	95.35	3178	
9	SB 5 % +PEG 25%+S 10%	113.57	3785	F2
10	SB 25 % +PEG 10%+S 5 %	102.67	3422	
11	SB 25 % +PEG 5 %+S 10%	125.56	4185	
12	SB 10 % +PEG 25 %+S 5%	98.45	3281	
13	SB 10 % +PEG 5 %+S 25%	105.68	3522	

Table Continued....

Sample	Conc mg/ml	Conc mg/ml	S. in fold
14	15%SB +25% S	175.45	5848
25	SO.ACT 25 % +PEG 5 %+S 10%	97.56	3252
26	SO.ACT 10 % +PEG 25 %+S 5%	158.89	5296
27	SO.ACT 10 % +PEG 5 %+S 25%	89.67	2989
28	15%SO.ACT +25% S	102.68	3422

Ftir study

FTIR graph obtaine from ftirintrumentsaples prepared by mixing of equipment with drug E.G with Glycrine, PH bubber4, buffer 7, gycerine, PEG 400 (Figure 2).

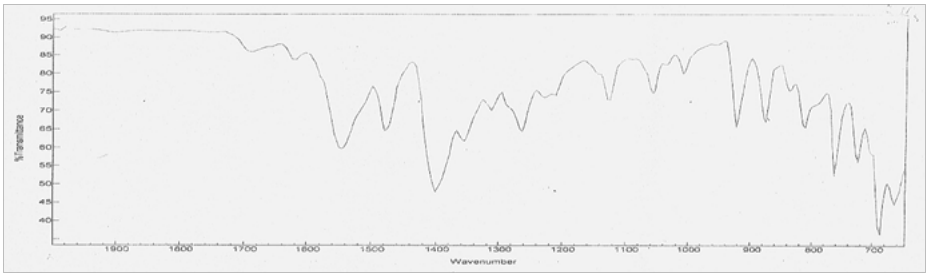

Figure 2 FTIR Graph of Flurbiprofen.

Procedure of batch manufacturing

a. Step 1: Weighing of drug: accurately 2gm under laminar air flow (Figure 3) (12-13mm of pressure) (at 22- 25°C temperature) (28-32 % of relative humidity).[8]

b. Step 2: Preparation of solvent system: the solvent system "s" comprise of PEG200, PEG400, glycerin, and propylene glycol in equal concentrations. Add drug to the solvent system with continuous stirring and flush nitrogen in the solution for 15mins (Figure 4).

c. Step 3: Washing: 5ml clear vials washed with dm water using auto jet vial washing machine (200 vials).

Wash room, and all other facility areas class 1, 00,000

Air locks to sterile area entry & manufacturing class 10,000

Sterile area class 1000

Storage, filling sealing area under LAF class 100

d. Step 4: Dry heat sterilization of vials: 100 vials are sterilized using drier at 200°C temperature for 3hr.

e. Step 5: Sterilization of filtration assembly and GBRS: wash 13mm grey butyl rubber stoppers with 0.1% teepol solution and make them foreign matter free, followed by washing with de-mineralized water to make them free from fibers and particulate matter. The filtration assembly sterilized before use, filter assembled in filtration assembly and autoclaved at 121°C temperature, 15lbs pressure, for 30mins)

f. Step 6: Filtration procedure: Filter the solution using 0.2 micron filtration assembly.

g. step 7: Filling of solution: 5ml accurate volume of solution filled in each vial using syringe under laminar air flow, (12-13mm of pressure laf) (at 22- 25°C temperature) (28-32% of relative humidity).

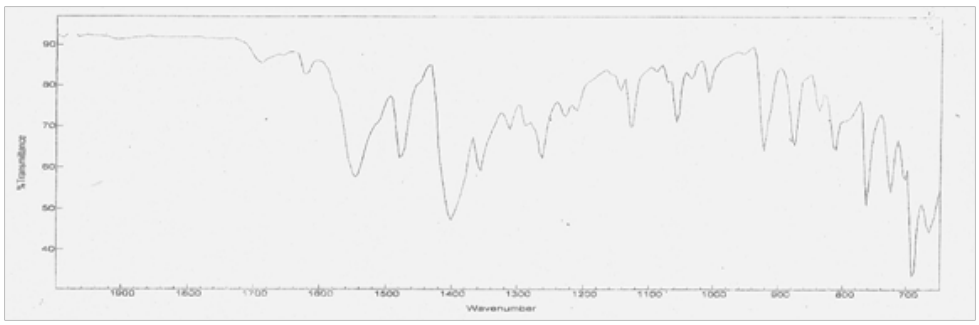

Figure 3 FTIR Graph of Flurbiprofen with PG.

Post formulation study

Assay: Reference Solution Preparation the 100ml of stock reference solution for each formulation was prepared. The composition of the reference[9] stock solution was similar to that of the respective formulations excluding the drug and also they were diluted similarly

as the formulation were diluted using water. This resulting solution is used as reference solution (blank) in comparison with prepared formulation to measure the % drug content by measuring absorbance suing UV spectrometer. The amount of flurbiprofen was determined from standard curve (Table 4).

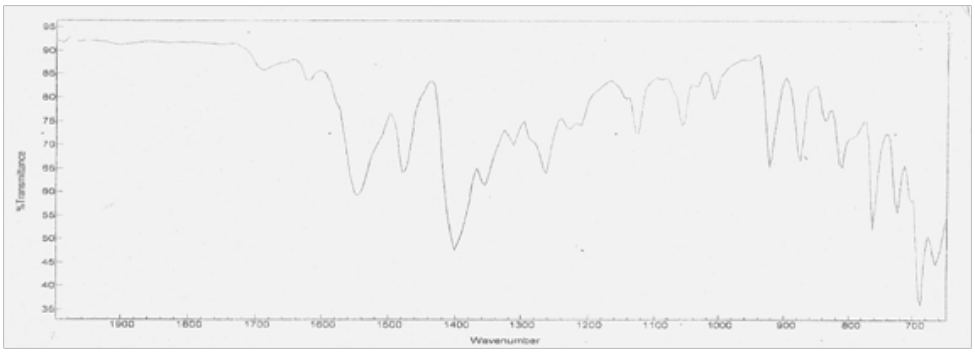

Figure 4 FTIR Graph of Flurbiprofen with PEG 400.

Table 4 The amount of flurbiprofen was determined from standard curve

Formulation	Drug content (Mg/Ml)	%Drug content
A (1 VIAL)	197	98.50%
B (1 VIAL)	203	101.50%
C (1 VIAL)	196	98%
D (1 VIAL)	201	100.50%

Dilution study: Precipitation of drug often occurs upon injecting a formulation into body fluid; the amount of precipitation can be correlated with the rate at which drug injected. Method for determination of such effect is dilution study. The serial dilutions of formulations were prepared in ration of 20:25 to 20:125 and stored at room temperature and examined visually foe the appearance of crystals and turbidity up to 24hrs (Table 5).[10]

Effect of PH: The 5ml of each prepared formulation 1 and 2 were kept at different temperature and/conditions such as refrigeration, room temperature, 37°C, 40°C,45°C.[11–14] At regular time interval the sample were examined for pH changes for 2weeks using digital pH meter (Table 6).

Table 5 Dilution study

Formulation	Dilution	Time in hours	
		Saline solution	5%W/V dextrosetime
A (3 VIALS)	10:25	- - - - - - - - - - - - - -	
	0.503472	- - - - - - - - - - - - - -	
	10:50	- - - - - - - - - - - - - -	
B (3 VIALS)	10:25	- - - - - - - - - - - - - -	
	0.503472	- - - - - - - - - - - - - -	
	10:50	- - - - - - - - - - - - - -	

Table 6 pH changes for 2 weeks using digital ph meter

Formulation	Withdrawal day	37 °c	40 °c	45 °c
One Vial From Each Batch	0	7.22	7.26	7.35
	2	7.21	7.24	7.32
	4	7.26	7.28	7.28
	6	7.21	7.27	7.29
(3 TEMP.*4 Batch) (12 Vials)	0	7.23	7.27	7.36
	2	7.22	7.25	7.33
	4	7.27	7.29	7.29
	6	7.22	7.28	7.31

Observation: Not more considerable changes found in both formulations, which indicate stability of both formulations. Extractable volume test: extractable volume should be not less than 5ml not more then 5.2ml (Table 7).

Table 7 Extractable Volume Should be not less than 5 Ml Not more than 5.2 Ml

S. no	Batch code	Vial checked	Volume
1	A	1	5.1
2	B	1	5.2
3	C	1	5
4	D	1	5.1

Viscosity: Viscosity levels had significant impact on perceived injection pain, specifically; less pain was associated with high viscosity. Visual check: after filling all vials checked for glass particles, black particles, white fibers, against black and white visual hoods.

BET test (bacterial endotoxin test): The gel-clot technique used for BET test. This method is a photometric test measuring increments in reactant turbidity. Result of BET TEST (Table 8).[15–17]

Table 8 Viscosity levels had significant impact on perceived injection pain, specifically; less pain was associated with high viscosity

S. no	Batch code	Viscosity
1	A	82
2	B	78
3	C	85
4	D	80

Sterility test: Method used-direct inoculation. Media-alternative thioglycolate media. Incubation time-14 days.

Stability study: 1 Vial from each batch stored at 25°c /60% rh, 5°c /30% rh, 40°c /65% rh, there is no change in physically, not found any color change (Table 11). After filling all vials checked for glass particles, black particles, white fibers, against black and white visual hoods (Table 9). The gel-clot technique used for bet test. This method is a photometric test measuring increments in reactant turbidity (Table 10).[18–20]

Table 9 After filling all vials checked for glass particles, black particles, white fibers, against black and white visual hoods

Formulation	Black fiber	White particle	Black particle	White fiber
A (10 VIALS)	No	No	YES	No
B (10 VIALS)	No	No	No	No
C (10 VIALS)	No	No	No	NO
D (10 VIALS)	No	YES	No	no

Table 10 The gel-clot technique used for bet test. this method is a photometric test measuring increments in reactant turbidity

Batch code of vial (One vial from each batch)	Turbidity	Conclusion
A	--	Sterile
B	--	Sterile
C	--	Sterile
D	--	Sterile

Table 11 Method used - direct inoculation. media-alternative thioglycolate media. incubation time-14 days

Batch (one vial from each batch)	Positive control	Negative control	Test product	Conclusion
A	+++	---	---	No Endotoxin Present
B	++	---	---	No Endotoxin Present
C	++	---	---	No Endotoxin Present
D	++	---	---	No Endotoxin Present

Conclusion

It appears from the outcomes that the watery dissolvability of Flurbiprofen was expanded more circumstances in hydrotropic mix specialists (PG25%+PEG10%+S5%), (SB5%+PEG25%+S10%) in hydrotropic arrangement which additionally utilized for group assembling and testing reason all cluster demonstrates great soundness and manufactured products show stable results. It is possible to make further more studies to develop for industrial manufacturing's.

Acknowledgements

None.

Conflicts of interest

Author declares that there is no conflict of interest.

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