DEVELOPMENT OF QUICK RELIEF ACECLOFENAC DRUG FORMULATIONS BY VARIOUS SOLUBILITY ENHANCEMENT APPROACHES

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Abstract. One of the widely prescribed analgesic in INDIA & worldwide and still standing in pharma market is aceclofenac. An attempt has been done to enhance solubility of drug by formulating three different quick relief formulations as tablets, films and gels as its major limitation is its solubility. The quick relief achieved by its disintegration, with the aid of superdisintegrants in the formulation in various concentrations. Six each of three different formulations such as solvent evaporation technique for films, sublimation technique for tablets and solid dispersion incorporation technique for gels were prepared & various parameters evaluated formulation wise. The optimized formulations from overall 18 formulations were found to be as T6, QF6 and G4 with percentage drug release 96.76%, 92.43% and 90.53% respectively.
Keywords: *super-disintegrants, quick relief formulations, sublimation, solid dispersion, solvent evaporation*

Introduction

Commonly seen prescribed analgesic drug aceclofenac, characterized for use in acute & chronic conditions of arthritis & osteoporosis. Major limitation is its solubility, belonging to BCS class II. This research focused on enhancement of its solubility to provide better results for easing pain. This research work has been aimed to please the patients of varied population in aspect of easiness and providing them with choice in formulations of the same drug. So, that they don't miss nor avoid the prescribed drug treatment. As pain is the most unpleasant sensation many don't wish to endure it for a longer time. At the same time look for quick relief dosage forms at any cost. Quick relief dosage forms are known with many synonyms like oral disintegrating, mouth melts, fastmelts etc., the dosage forms like tablets, films and gels are general preparations incorporated with superdisintegrants for quick disintegration and dissolution on immediate contact with liquid. Thus bioavailability is also reached quickly and starts giving relief instantly. The formulation of any quick releasing formulations depend upon the superdisintegrants incorporation and also the solubility enhancers for enhancing faster disintegration of the prepared formulations and absorption of the disintegrated particles into systemic circulation.

In the present study aceclofenac drug is not water soluble and the preparation of quick release formulation of it requires combination of excipients for its solubility enhancement used is urea, between 80 citric acid is used as flavour enhancer,

sequestering agent and for antioxidant properties, camphor used as sublimating agent in the quick relief tablet formulations with its vapourization properties it creates spaces and hence enhance the faster disintegration of the formulation polyethylene glycol used as plasticizer for formulating quick relief films. Magnesium stearate used as lubricant in the quick relief tablet formulation. Sodium starch glycollate is used as disintegrant, colloidal silicon dioxide is used as stabilizing agent and adsorbent, talc as lubricant, sucrose as sweetening agent, HPMC E15, HPMC K4M used for film formation and viscosifying agents, maltodextrin as viscosity enhancer, glycerin as humectant, alcohol as cosolvent, PVPK30 as binder, dextrose as sweetening agent. With the applications of excipients the suitability of their use in the dosage form utilized in various ratios until optimized formulation is identified by specific evaluation parameters.

Literature review

Bin Roslan and Widodo (2023) in article stated the current challenges and prospects of developing metformin odt's. Woyna-Orlewicz et al. (2023) highlighted the use co-processed excipients like F-melt M, Ludiflash, Pharmabust 500, prosolv, ODT G2 and evaluated formulations for characteristics of powder compaction, true density and tablet speed sensitivity. Gupta et al. (2023) stressed on the facts of benefits of ODT formulations over conventional tablets. Juan et al. (2023) developed ivermectin oral disintegrating tablets using factorial design i.e., by design of experiments. Garrepally and Rao (2014) in design, development & evaluation of stomach specific insitu gel for antibiotics cefdinir prepared gastroretentive insitu gels of cefdinir using natural biodegradable polymers. Arun Gokul et al. (2015) developed aceclofenac gel using carbopol 934, HPMC K15 etc. polymers. Guleri and Preet (2013) formulated topical aceclofenac gels to overcome the side effects associated with other conventional dosage forms. Jana et al. (2014) developed topical aceclofenac-crospovidone gel by quality by design approach i.e., 32 factorial design. Shukla et al. (2009) developed and evaluated sublingual tablets of fixed dose as therapy for treating hypertension & anxiety using bisoprolol fumarate (antihypertensive drug) and buspirone hydrochloride (anti-anxiety drug) without need of swallowing. Bhise et al. (2008) prepared and evaluated oral effervescent & dispersible formulations of diphenhydramine hydrochloride using Indion 234 & Tulsion 343 containing polyacrylic backbone with cation exchange resins successfully developed for taste masking of the drug. Shah and Mashru (2008) formulated oral reconstitutable suspension powder as cachets of immense bitter drug primaquine phosphate using beta-cyclodextrin. Patel and Vavia (2008) studied the potential ternary combination of drug, cyclodextrin and polymer as successful development of taste masked oral formulation approach. Khan et al. (2007) formulated & evaluated rapid disintegrating tablets of ondansetron HCL by precipitation method and taste masked by complexing with aminoalkyl methacrylate copolymer of various ratios and optimized it. Bora et al. (2008) formulated taste masked microspheres of bitter drug by spray-drying method using three polymers chitosan,eudragit E 100, methocel E15 LV in various ratio's and evaluated for taste masking & releasing properties. Ogawa et al. (2004) presented in his study the degree of quantifying suppression of bitterness of two aminoacids namely L-phenylalanine & L-isoleucine using various chemicals. Elzainy et al. (2004) developed and evaluated antihistamine drug cetrizine topical multilamellar vesicles formulations for its faster degree of suppression. Korsgren et al. (2007) did comparative studies on antihistamine drug cetrizine for oral and intranasal formulations for its efficacy against allergic rhinitis.

Wood et al. (1987) did investigational studies on the metabolism and pharmacokinetic studies on new H1 antihistamine drug. Cilurzo et al. (2008) developed and evaluated fast dissolving films of maltodextrins using glycerin as plasticizer and optimized it. Dinge and Nagarsenker (2008) formulated and evaluated triclosan fast dissolving films using poloxamer 407 and HPBCD as polymers. Jain et al. (2018) in review article detailed about the applications of fast dissolving films over capsules, tablets and potential use in various disease conditions of cough, pain etc. Mashru et al. (2005) formulated and evaluated the fast dissolving films of salbutamol sulphate for treatment of asthma condition. Ali and Quadir (2007) in his study explored the use of high molecular weight povidone polymers for the formulation of fast dissolving films.

Materials and Methods

The FTIR study was carried out to determine the physical and chemical interaction between Aceclofenac and excipients used. IR spectra were recorded for Aceclofenac & their formulations reveal that no physical and chemical interaction was found between them. Saliva simulating fluid prepared using 13.872g of dihydrogen potassium phosphate in a measured small quantity of distilled water taken from 1000ml distilled water beaker. To it added 35.084g of disodium hydrogen phosphate stirred continuously until a clear solution formed then made upto 1000ml with the distilled water. 100mg of pure drug aceclofenac was dissolved in measured small quantity of methanol taken in 100ml volumetric flask then made upto the mark with saliva simulating fluid. This is primary stock solution with 1000ug/ml concentration. From this primary stock solution, 10ml was drawn into 100ml volumetric flask and diluted upto the mark using saliva simulating forming secondary stock solution. From it subsequent dilutions were done to obtain 2ug/ml, 4ug/ml, 6ug/ml and 8ug/ml. their absorbancies were measured using UV-Visible spectrophotometer at 276nm. The materials involve are Aceclofenac that was received as a gift sample from CIPLA. Camphor, Sucrose, Sodium crosscarmellose, Potassium dihydrogen phosphate, Disodium hydrogen phosphate, Sodium starch glycollate, Colloidal silicon dioxide, Mannitol, Magnesium stearate, Maltodextrin, HPMC E15, HPMC K4M, Citric acid, Tween 80, PEG 400, Glycerin, Dextrose, PEG 6000, Urea, PVP K 30, Sodium alginate were purchased from SD fine chem Ltd. According to the requirements mentioned in *Table 1* all the ingredients are passed through sieve no. 100 priorly. Firstly coherent wet mass of drug along with 10% PVP alcoholic solution prepared then passed through sieve no.16 and dried in tray dryer for 30 min separately. Remaining formulations containing sublimating agent T3-T6 dried for 8 hrs. Finally all the granules along with magnesium stearate & talc added for compression into tablets.

Table 1. *Formulation of quick relief tablets.*

Ingredients	Formulations					
	T1	T2	T3	T4	T5	T6
Aceclofenac (mg).	100	100	100	100	100	100
Camphor (mg).	-	-	12.5	12.5	25	25
Sucrose (mg).	2.5	2.5	2.5	2.5	2.5	2.5
Sodium Cross Carmellose (mg).	-	15	-	15	-	15
Sodium starch glycolate (mg).	15	-	15	-	15	-
Colloidal silicon dioxide (mg).	-	-	-	-	2.5	2.5
Mannitol q.s. (mg).	132.5	132.5	120	120	105	105
Total weight(mg)	250	250	250	250	250	250

These were prepared as mentioned in *Table 2* using solvent casting method in which firstly polymer having water solubility or as mixture dissolved in solvent to get viscous transparent solution. Then the remaining ingredients dissolved using magnet stirrer for uniform mixing. This clear solution was put under vacuum to remove air bubbles. This solution was the poured into a glass mould or petridishes in oven at 40-500c for drying of films checked periodically. In this as mentioned in *Table 3*, first, polymer was melted at 80-850c for few minutes then aceclofenac was added to form mixture followed by quick cooling. The solidified mass was dried, pulverized & passed through sieve no.44 and stored in desiccator until utilized. Secondly gel base was prepared by polymer dispersion in measured quantity of distilled water and left for 8hr swelling. To this dispersion incorporated solid dispersion slowly followed by adding remaining ingredients forming gel solid dispersions. For quick relief tablets thickness, hardness, friability (%), weight variation, drug content tests for all the tablet formulations were determined using Vernier calliper's, Monsanto hardness tester and UV-visible spectrophotometer were used for determining the percentage drug release. The percentage drug release was found to be at the end of 30 min as 53.48, 61.24, 63.47, 78.72, 91.24 & 96.47% for T1-T6 respectively. The results recorded in *Table 4* and *Table 5*. For quick relief films evaluation tests such as weight variation, drug content uniformity, surface pH, folding endurance, dissolving time & invitro drug release of the film assayed spectrophotometrically at 275nm.The results recorded in *Table 6* and *Table 7*. For quick relief oral gels: tests such as general appearance, pH, homogeneity, texture and percentage invitro drug release evaluations done for all formulations were performed and recorded in *Table 8*.

Table 2. *Formulation of quick relief films.*

No.	Formulation Ingredients	Quantity (mg)					
		QF1	QF2	QF3	QF4	QF5	QF6
1	HPMC E15(mg)	-	-	-	400	400	400
2	HPMC K4M(mg)	400	400	400	-	-	-
3	Maltodextrin(mg)	-	-	100	-	-	100
4	Drug(mg)	100	100	100	100	100	100
5	Citric acid(mg)	10	10	10	10	10	10
6	Tween 80(ml)	0.5	0.5	0.5	0.5	0.5	0.5
7	PEG 400(ml)	0.4	0.4	0.4	0.4	0.4	0.4
8	Glycerin(ml)	0.5	0.5	0.5	0.5	0.5	0.5
9	Water(ml)	10	-	10	10	-	10
10	Alcohol(ml)	10	10	10	10	10	10

Table 3. *Formulation of quick relief oral gels.*

No.	Formulation Ingredients	Quantity (mg)					
		G1	G2	G3	G4	G5	G6
1	Maltodextrin (mg).	500	-	-	-	-	-
2	Sodium alginate (mg).	-	500	500	500	500	500
3	Drug (mg).	100	100	100	100	100	100
4	Sodium starch glycollate (mg).	-	100	-	-	-	-
5	PEG 6000(mg).	-	-	100	-	-	-
6	Urea (mg).	-	-	-	100	-	-
7	Mannitol (mg).	-	-	-	-	100	-
8	PVP K30 (mg).	-	-	-	-	-	100
9	Dextrose (mg).	q.s	q.s	q.s	q.s	q.s	q.s
10	Preservatives.	q.s	q.s	q.s	q.s	q.s	q.s
11	Water.	10ml	10ml	10ml	10ml	10ml	10ml

Table 4. *Evaluation parameters of formulations T1-T6.*

Formulation code of the tablets	Tablet thickness (mm)	Tablet weight variation (%)	Tablet hardness (kg/cm^2)	Tablet friability (%)	Drug content present in tablet (%)
T1	4.6	0.2	4.0	0.47	95
T2	4.6	0.2	4.0	0.43	94
T3	4.6	0.24	3.8	0.4	95
T4	4.6	0.16	3.8	0.4	97
T5	4.6	0.18	3.5	0.4	97
T6	4.6	0.16	3.5	0.4	97

Table 5. *Dissolution release profile of formulations T1-T6.*

No.	Time (min)	In vitro percentage release of drug (%)					
		T1	T2	T3	T4	T5	T6
1	5	37.83	38.71	55.8	51.68	56.95	53.48
2	10	41.44	61.97	58.97	64.8	58.41	61.24
3	15	56.18	64.97	70.58	71.57	66.9	63.47
4	20	63.47	77.18	82.11	75	78	78.72
5	25	75.6	80.27	84.72	87.34	88.45	91.24
6	30	83.1	85.8	86.74	88.54	93.72	96.47

Table 6. *Comparative dissolution release profile of formulation QF1-QF6.*

No.	Time (min)	In vitro percentage release of drug (%)					
		QF1	QF2	QF3	QF4	QF5	QF6
1	5	45.43	57.34	57.40	49.31	62.47	58.58
2	10	52.33	61.98	61.76	54.16	65.21	65.00
3	15	53.46	62.09	66.40	63.81	69.69	72.60
4	20	60.36	69.26	70.33	68.45	92.92	78.64
5	25	75.67	71.95	71.95	88.23	94.27	88.28
6	30	80.74	82.95	76.21	90.22	95.99	92.43

Table 7. *Evaluation parameters of quick relief films.*

No.	Evaluation parameters	Formulation					
		QF1	QF2	QF3	QF4	QF5	QF6
1	Weight variation (mg)	60	62	62	62	61	63
2	Surface pH	6.7	6.7	6.73	6.7	6.7	6.78
3	Folding endurance	52	79	22	47	19	84
4	Drug content (%)	80	85.3	83	86	87.3	90
5	Disintegration time(sec)	11	7	9	10	5	8

Table 8. *Dissolution release profile of quick relief oral gels formulations G1-G6.*

Time (min)	In vitro percentage drug release (%)					
	G1	G2	G3	G4	G5	G6
5	46.84	56.70	48.17	62.85	42.60	43.97
10	62.16	63.10	58.37	69.27	58.90	44.8
15	63.20	64.8	61.22	72.65	66.33	45.99
20	70.03	66.98	80.38	79.26	76.21	48.54
25	72.83	77.5	81.75	81.67	78.33	66.7
30	80.97	80.31	82.44	90.53	86.61	68.19

Results and Discussion

The standard graph of Aceclofenac has shown good linearity with R2 Value 0.9943 in Saliva Simulating Fluid pH 6.8 (*Table 9* and *Figure 1*). The FTIR study was carried out to determine the physical and chemical interaction between Aceclofenac and excipients used (*Figure 2* to *Figure 19*). IR spectra were recorded for Aceclofenac and their formulations reveal that no physical and chemical interaction was found between them and *Figure 2* to *Figure 4* results of the optimized formulations provided. The evaluated parameters specific for 18 quick relief formulations each dosage form such as tablets, films and gels which can be bioavailable at a faster rate & show action were detailed as all the formulated tablets by sublimation method were of uniform thickness, exhibiting low weight variation, hardness in range of 3-4 kg/cm2. The percentage tablet friability of all found to be less than 1.The key excipient used as camphor improved porosity nature in tablets giving enhanced saliva penetration thereby quick disintegration & action achieved. The highest % invitro drug release was found to be T6 with 96.47%. The quick relief films formulated by solvent evaporation method found no tackiness. Weight variation and folding endurance ranged between 60-63mg & 19-84 respectively. All have neutral surface pH. The % invitro drug release was found in the order as follows QF3<QF1<QF2<QF4<QF5<QF6. This was achieved due to addition of low viscous polymer HPMC E15 & MDX combination in F6 being absorbed rapidly. Finally quick relief gels formulated by solid dispersions of drug & excipient for solubility enhancement then were incorporated into gel base. The optimized formulation found as G4 containing solid dispersion, urea & Aceclofenac in ratio of 1:5 showed greater drug release because of its enhanced solubility. Thus providing quick relief as it gets absorbed in the oral cavity. All the above three types of formulations are patient friendly irrespective of their age (pediatrics, geriatrics and adults) who wishes to have a change in taking routine medications.

Table 9. *Standard graph of Aceclofenac using saliva simulating fluid pH (6.8).*

No.	Concentration of pure aceclofenac drug (µg/ml)	Absorbance (nm)
1	0	0.0000
2	10	0.2341
3	20	0.3433
4	30	0.5872
5	40	0.7805
6	50	0.9537

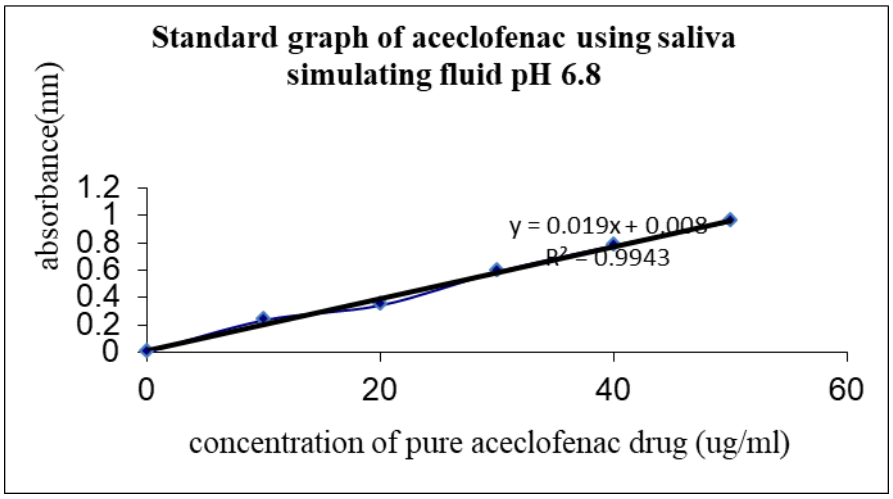

Figure 1. *Standard graph of aceclofenac drug using Saliva simulating fluid pH (6.8).*

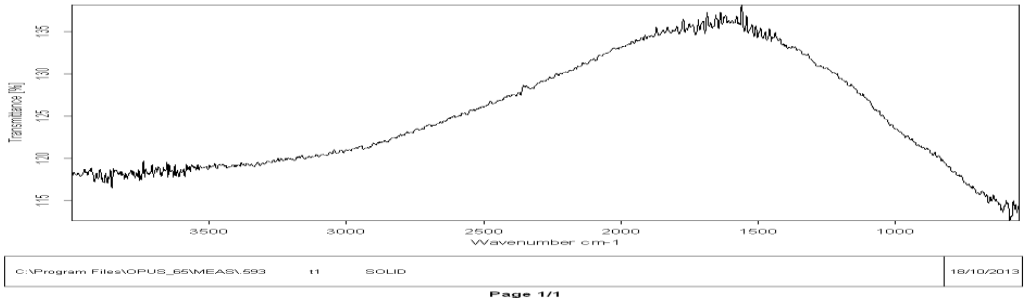

Figure 2. *FTIR of formulation T1.*

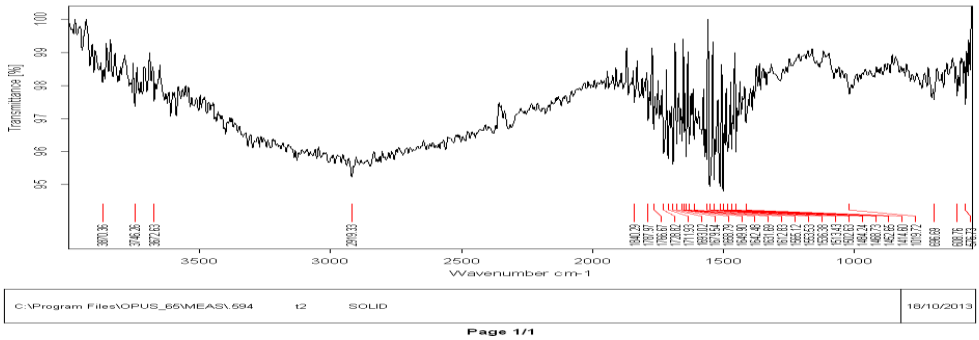

Figure 3. *FTIR of formulation T2.*

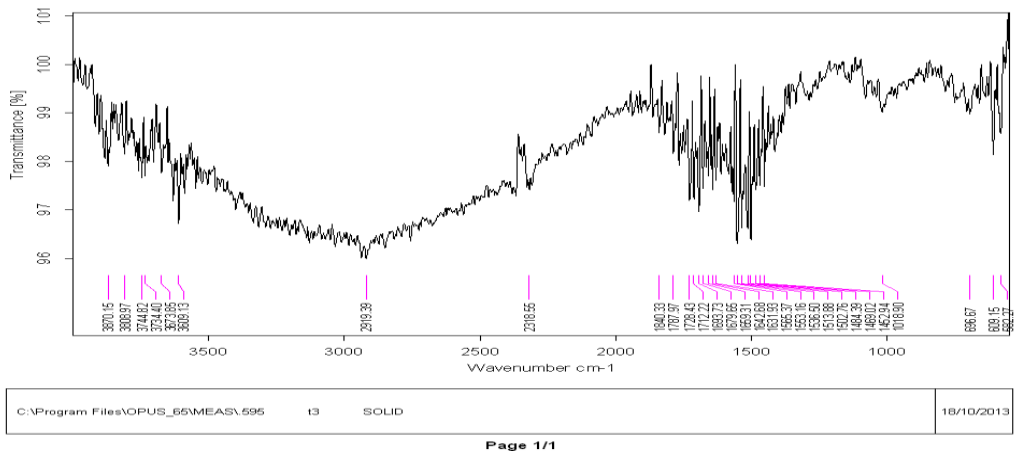

Figure 4. *FTIR of formulation T3.*

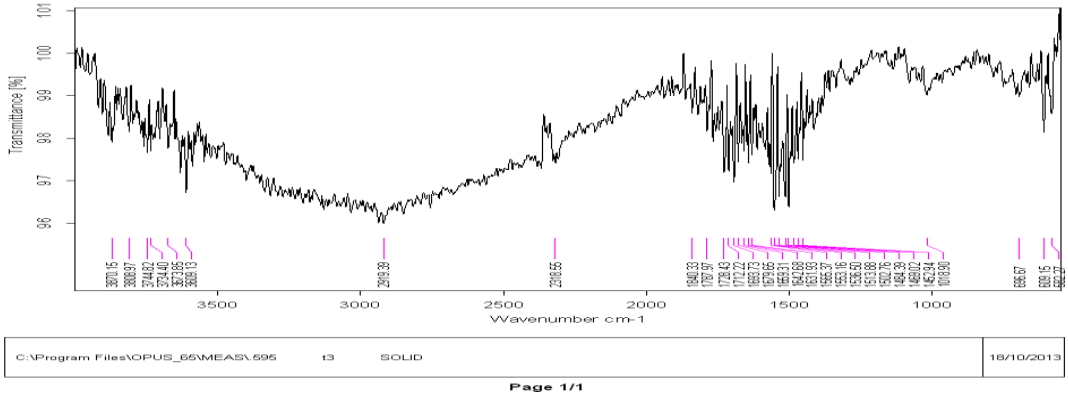

Figure 5. *FTIR of formulation T4.*

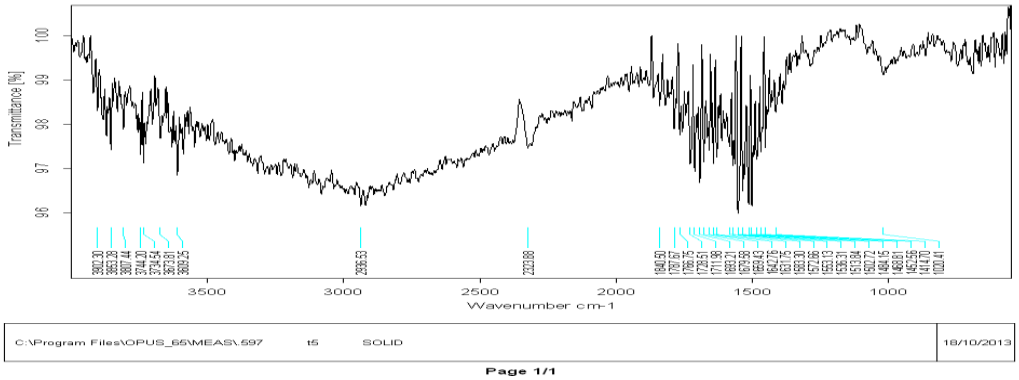

Figure 6. *FTIR of formulation T5.*

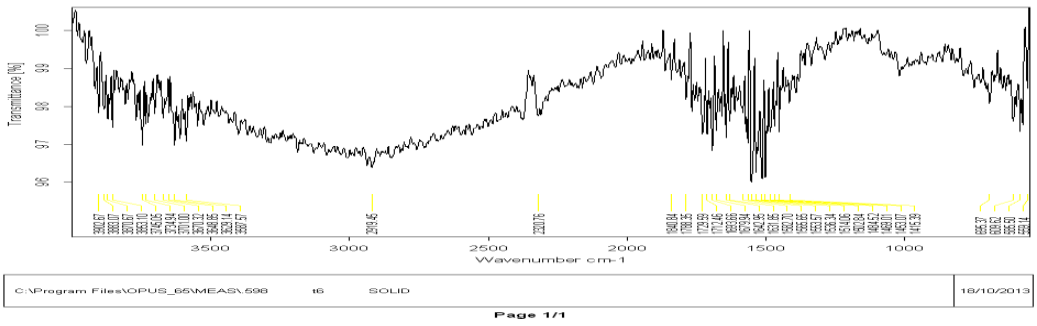

Figure 7. *FTIR of formulation T6.*

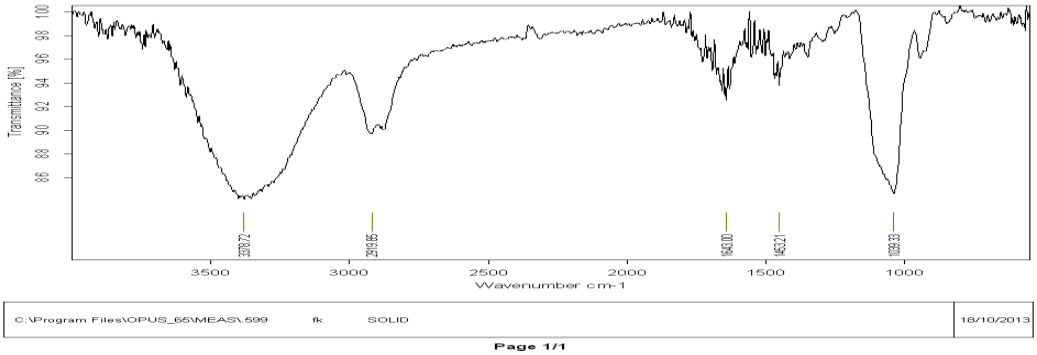

Figure 8. *FTIR of formulation QF1.*

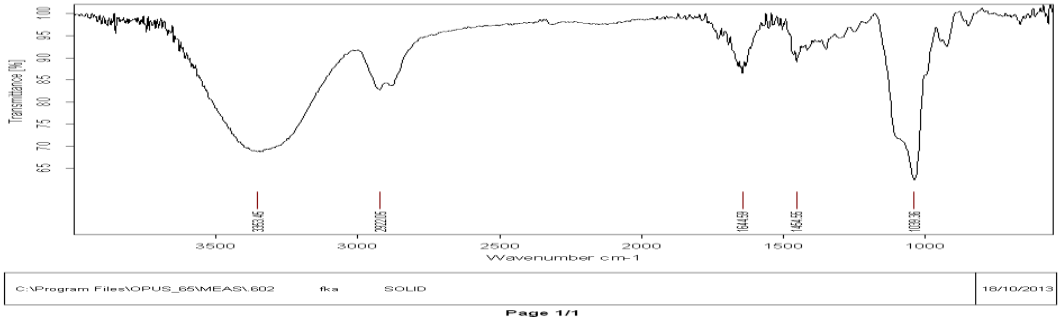

Figure 9. *FTIR of formulation QF2.*

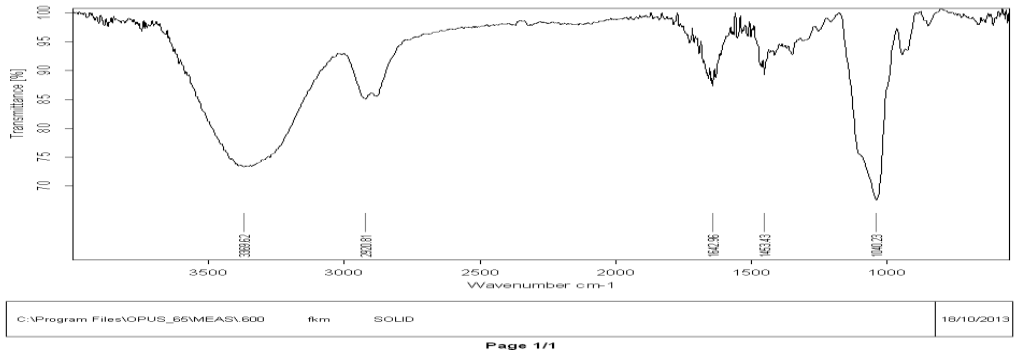

Figure 10. *FTIR of formulation QF3.*

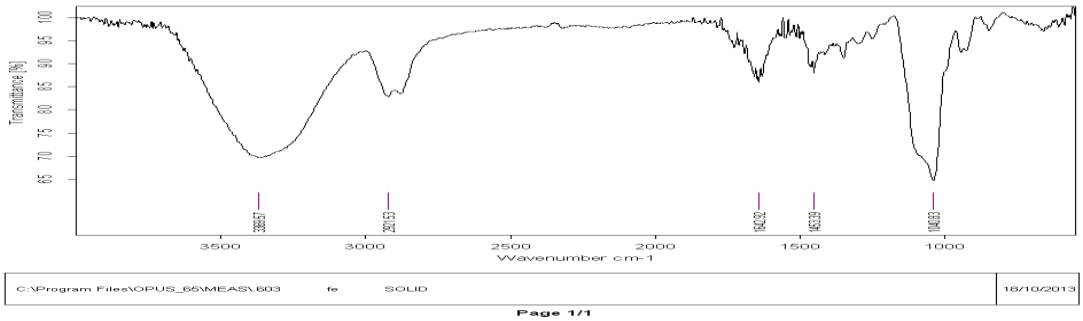

Figure 11. *FTIR of formulation F4.*

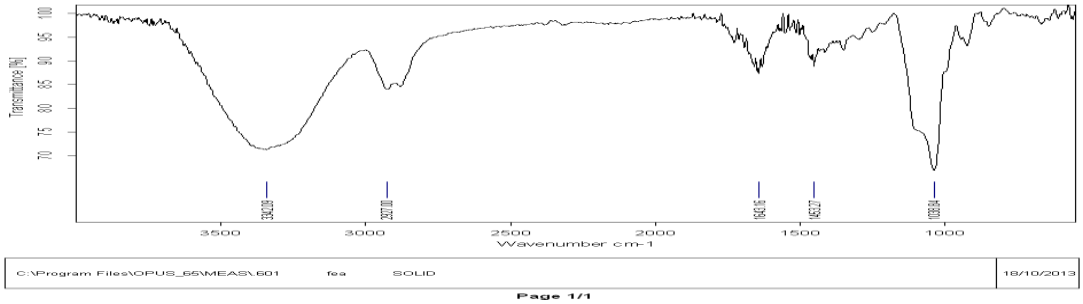

Figure 12. *FTIR of formulation QF5.*

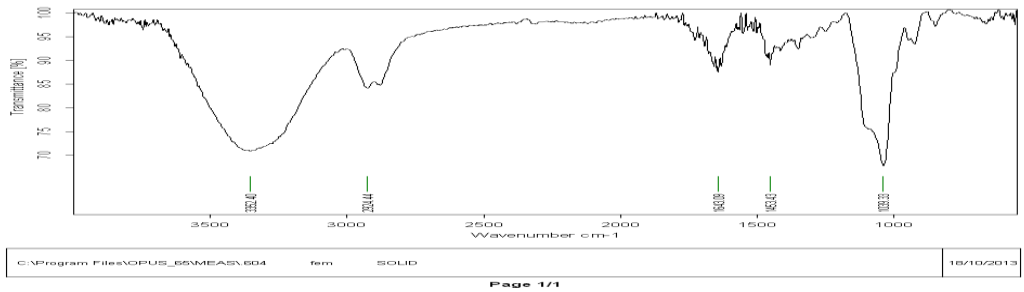

Figure 13. *FTIR of formulation QF6.*

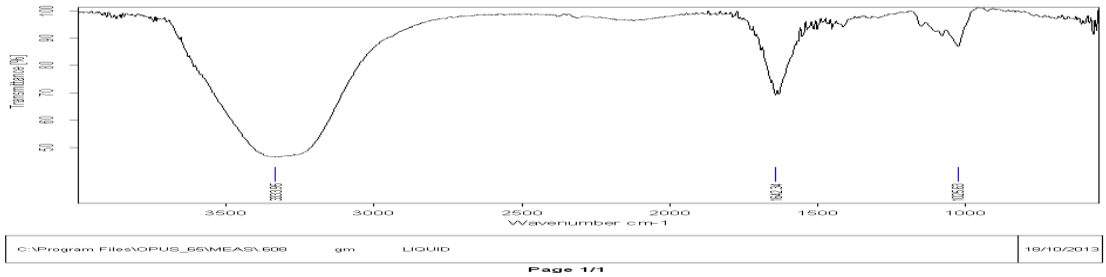

Figure 14. *FTIR of formulation G1.*

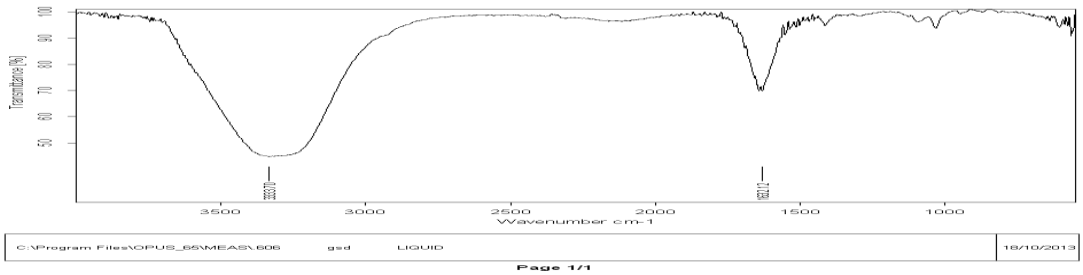

Figure 15. *FTIR of formulation G2.*

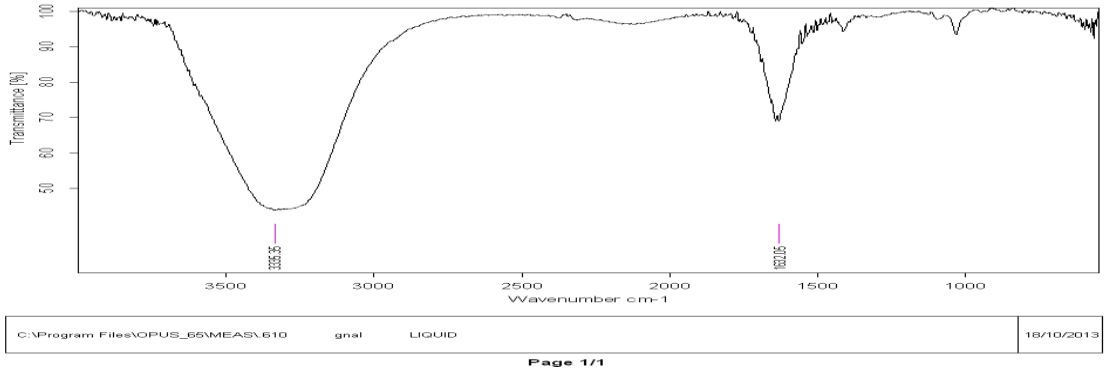

Figure 16. *FTIR of formulation G3.*

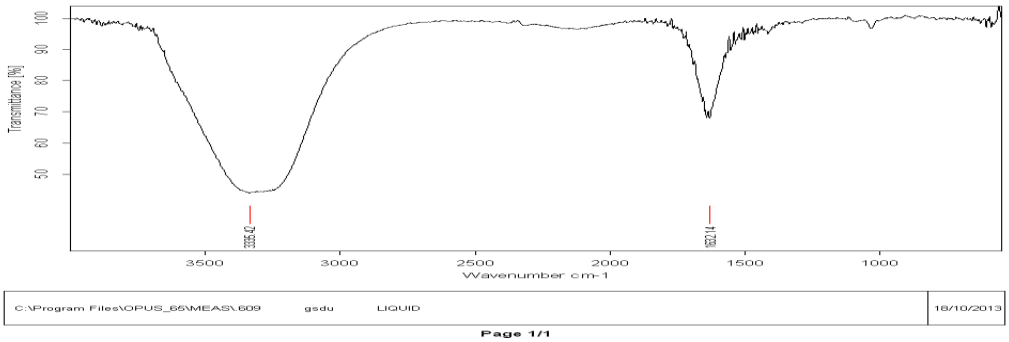

Figure 17. *FTIR of formulation G4.*

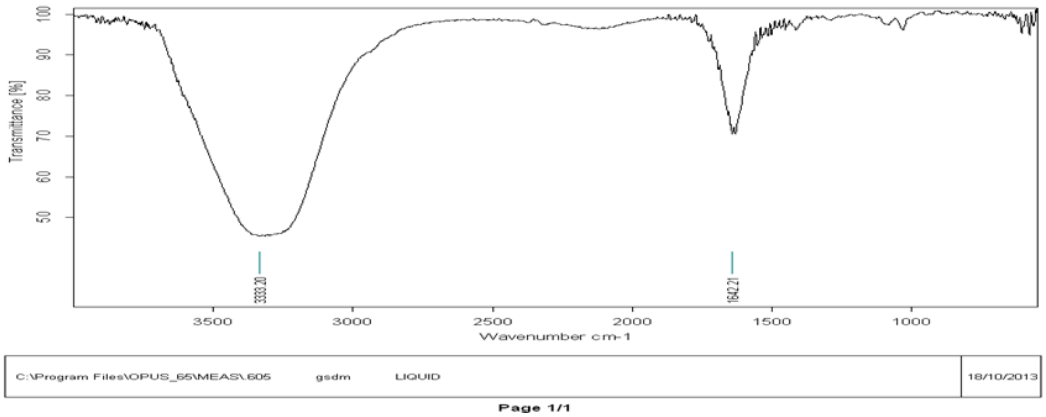

Figure 18. *FTIR of formulation G5.*

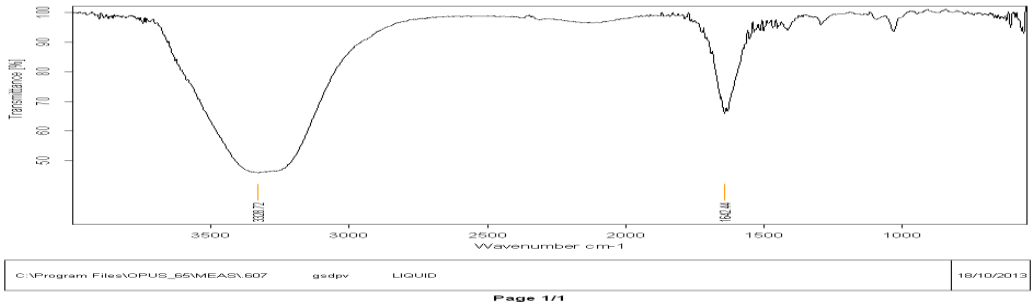

Figure 19. *FTIR of formulation G6.*

Conclusion

The present research focused on improving the solubility in three different formulation of analgesic drug. Aceclofenac as quick relief dosage forms-tablets, films, gels using novel techniques solvent evaporation, solid dispersion incorporation & sublimation. Satisfactory results were observed and this approach can be applied for further studies in improving the formulation for patients giving quick relief from enduring something unpleasant by exploring various excipients & methodologies.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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