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In vitro alcohol induced dose dumping studies for Quetiapine fumarate floating drug delivery systems

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Abstract

Alcohol dose dumping can occur due to the solubility of the pharmaceutical excipients, the solubility of the drug, and the formulation's drug release mechanism. Cellulosics are the most commonly used polymers in pharmaceutical controlled release technologies. The ethanol vulnerability of tablets made with HPMC K250, HPMC K750 and HPMC K1500 were investigated with the low soluble drug quetiapine fumarate. Quetiapine fumarate is an antipsychotic drug and it is suitable drug candidate for FDDS due to its solubility in low pH. HPMC K250, HPMC K750 and HPMC K1500 were used as a polymer matrix to control the release of quetiapine fumarate up to 24 hr. The quetiapine floating tablets were prepared by direct compression method. All the tablets were evaluated for the Pre-compression and post Compression Parameter. In-vitro dissolution study was done in Normal Dissolution Media, 0.1N Hcl and also in 10%, 20%, 30% and 40% v/v hydro alcoholic media for up to 24 hrs. All HPMC K250, HPMC K750 and HPMC K1500 preparation did not fail in alcoholic media. From these studies it was concluded that the concern around alcohol dose dumping seems negligible for these polymers.

Keywords: Quetiapine fumarate; Dose dumping; Controlled Release Polymer; Floating drug delivery system (FDDS); Hydroxy propyl methyl cellulose (HPMC)

1. Introduction

Alcoholic beverages have been consumed for thousands of years, world health organization or the WHO released its global status report on alcohol and health. According to the report, about 38.3% of the world's population is consume alcohol regularly. In another report, US statistical data showed that around 50% of the American population routinely consumed alcoholic beverages[1]. The potential effect of alcoholic drinks in significantly accelerating drug release from modified release dosage formulations has been of some concern. It is known that alcohol has an influence on the absorption, metabolism and excretion of drugs, which can potentially lead to adverse side effects. Toxicity is most often associated with acute intake rather than longer-term consumption of alcohol, but both patterns can impact the toxic-kinetics of concomitantly administered medicines. Unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form is often referred to as "dose dumping". Depending on the therapeutic indication and the therapeutic index of a drug, dose-dumping can pose a risk to patients significantly, either due to safety issues or diminished efficacy or both. Some modified-release oral dosage forms contain drugs and excipients that exhibit higher solubility in ethanolic solutions compared to water. Such products can be expected to exhibit a more rapid drug dissolution and release rate in the presence of ethanol. Therefore, in theory, concomitant consumption of alcoholic beverages along with these products might be expected to have the potential to induce dose dumping.

Quetiapine Fumarate (QF) is a psychotropic agent indicated for the treatment of schizophrenia and manic episodes associated with bipolar disorder. QF having good solubility in aqueous solvents and ethanol. However, rapid release of

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drug in a lesser period of time, over-all amount[2], or a significant amount of the drug from a prolonged release dosage form is often referred to as "dose dumping". United States FDA's viewpoint on the dose dumping in general for modified-release dosage forms in the presence of alcoholic beverages and FDA's efforts to reduce the regulatory burden and avoidable human studies in generic drug development. Dose dumping can pose a major risk[3] to patients either due to the safety concerns or decrease efficacy or both. HPMC custom grades has been used as a controlled release agent. The quetiapine tablets prepared during screening with HPMC alone as a polymer for tablet matrix resulted tablets were observed for dose dumping in the presence of alcohol.

The objective of the investigation was to optimize novel polymers concentration in quetiapine prolonged release tablets 200 mg. The role of novel polymers concentration in tablet matrix resisting the alcohol-induced dose dumping was estimated. All the formulations were evaluated for dissolution in 0.1 N hydrochloric acid with and without ethanol.

2. Material and methods

2.1. Materials

Quetiapine Fumarate was procured from MSN Labs Ltd. Hyderabad. HPMC K250 PH PRM, HPMC K750 PH PRM, HPMC K1500 PH PRM, and Polyox WSR 301 were obtained from Ashland India, Pvt., Ltd. Sodium bicarbonate, Avicel PH 102, PVP K 30, talc and magnesium stearate were procured from SD Fine Ltd. All other chemicals used were of analytical grade.

2.2. Methods

2.2.1. *Formulation method*

Accurately weighed quantities of polymers and MCC were taken in a mortar and mixed geometrically, to this required quantity of quetiapine fumarate was added and mixed slightly with pestle. Accurately weighed quantity of sodium bicarbonate was taken separately in a mortar[4] and powdered with pestle. The powder is passed through sieve no 40 and mixed with the drug blend which is also passed through sieve no 40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this magnesium stearate was added and mixed for 5 minutes, later talc was added and mixed for 2 minutes. The mixture equivalent to 400 mg was compressed into tablets with 10 mm round concave punches at a hardness of 6 kg/cm^2.

Table 1 Composition of floating matrix tablets of quetiapine fumarate with HPMC K250 PH PRM

Ingredients (weight in mg)	**Formulations**						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Quetiapine fumarate*	230.4	230.4	230.4	230.4	230.4	230.4	230.4
HPMC K250 PH PRM	65	70	75	80	85	90	95
WSR 301	13.6	13.6	13.6	13.6	13.6	13.6	13.6
Sodium bicarbonate	22	24	26	28	30	32	34
Avicel PH 102	53	46	39	32	25	18	11
PVP K 30	12	12	12	12	12	12	12
Talc	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2
Total weight	400	400	400	400	400	400	400

Quetiapine Fumarate* is equivalent to 200mg of quetiapine

Table 2 Composition of floating matrix tablets of quetiapine fumarate with HPMC K750 PH PRM

Ingredients (weight in mg)	Formulations						
	F8	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**
Quetiapine fumarate*	230.4	230.4	230.4	230.4	230.4	230.4	230.4
HPMC K750 PH PRM	65	70	75	80	85	90	95
WSR 301	13.6	13.6	13.6	13.6	13.6	13.6	13.6
Sodium bicarbonate	22	24	26	28	30	32	34
Avicel PH 102	53	46	39	32	25	18	11
PVP K 30	12	12	12	12	12	12	12
Talc	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2
Total weight	400	400	400	400	400	400	400

Quetiapine fumarate* is equivalent to 200mg of Quetiapine

Table 3 Composition of floating matrix tablets of quetiapine fumarate with HPMC K1500 PH PRM

Ingredients (weight in mg)	Formulations						
	F15	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**
Quetiapine fumarate*	230.4	230.4	230.4	230.4	230.4	230.4	230.4
HPMC K1500 PH PRM	65	70	75	80	85	90	95
WSR 301	13.6	13.6	13.6	13.6	13.6	13.6	13.6
Sodium bicarbonate	22	24	26	28	30	32	34
Avicel PH 102	53	46	39	32	25	18	11
PVP K 30	12	12	12	12	12	12	12
Talc	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2
Total weight	400	400	400	400	400	400	400

Quetiapine fumarate* is equivalent to 200mg of quetiapine

2.3. Evaluation of floating matrix tablets of quetiapine fumarate

Evaluation parameters like weight variation, thickness, hardness, friability *In vitro* buoyancy studies and drug content was performed according to the reported methods.

2.3.1. *In vitro drug release studies*

The *In vitro* drug release study was performed for the single & multiple-unit tablets using USP Type II dissolution apparatus using 900 ml of 0.1N HCl at a temperature of 37±0.5 ºC at 50 rpm. 5 ml of sample was collected at 0, 2, 4, 6, 8, 12, 16, 20, 24 hours and the same volume of fresh media was replenished. The drug content in the samples was estimated using UV visible spectrophotometer at 231 nm.

Alcoholic dose dumping study was carried[5,6] out indifferent concentration of hydro alcoholic media

Where;
10 % v/v hydro alcoholic media indicates 810 ml 0.1N HCl+ 90 ml Ethanol

20 % v/v indicates 720 ml 0.1N HCl+ 180 ml Ethanol
30 % v/v indicates 630 ml 0.1N HCl + 270 ml Ethanol
40 % v/v indicates 540 ml 0.1N HCl+ 360 ml Ethanol[7]

2.3.2. *Drug-excipient compatibility studies*

Fourier transform infrared spectroscopy (FTIR)

The spectral analysis can be used to identify the functional groups in the pure drug and drug-excipient compatibility. Pure quetiapine fumarate FTIR spectra, physical mixtures and optimized formulation were recorded by using FTIR (SHIMADZU). Weighed quantity of KBr and drug-excipients were taken in the ratio 100 : 1 and mixed by mortar. The samples were made into pellet by the application of pressure. Then the FTIR spectras were recorded in the wavelength region between 4000 and 400 cm^{-1}.

3. Results and discussion

The evaluation parameters like weight variation, thickness, hardness, friability and drug content were evaluated and found to be within the IP limits. The floating lag time of all the formulations were found to be within 31-48 seconds and formulation F19 was found to be least lag time of 31 sec, and all the formulations shown more than 24h of total floating time.

3.1. *In vitro* dissolution studies

Table 4 *In vitro* drug release profile of quetiapine fumarate floating tablets F1-F7

Time(h)	F1	F2	F3	F4	F5	F6	F7
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
2	04.22±1.23	04.13±1.24	04.65±1.52	09.24±1.78	07.19±.15	05.27±1.19	04.51±1.21
4	12.04±1.34	13.01±1.15	15.12±1.29	26.95±0.29	22.15±0.88	21.95±2.22	18.71±2.25
6	23.05±1.68	28.49±1.44	33.34±1.82	40.09±1.29	39.18±0.78	38.09±1.78	36.24±1.75
8	34.06±1.38	37.32±1.58	40.12±2.29	50.72±1.16	44.81±1.75	43.72±1.28	42.80±1.52
12	42.94±1.24	46.83±2.24	51.72±1.27	61.77±0.29	57.49±2.28	55.77±1.32	53.50±0.52
16	54.88±1.66	63.49±1.78	65.45±1.19	72.36±0.27	70.57±0.19	69.36±2.26	68.69±0.86
20	68.74±1.45	71.28±1.59	74.56±1.27	83.23±0.27	80.21±0.32	78.23±2.29	76.69±1.77
24	76.34±1.32	79.21±1.52	86.29±1.22	94.34±0.29	91.34±0.25	88.48±1.17	86.88±1.16

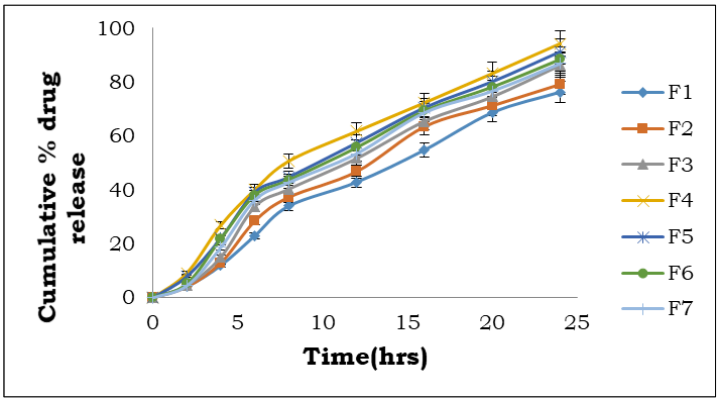

Figure 1 *In vitro* drug release profile of quetiapine fumarate floating tablets F1-F7 in 0.1N Hcl

Table 5 *In vitro* Drug Release Profile of Quetiapine Fumarate floating tablets F8-F14in 0.1N Hcl

Time (h)	F8	F9	F10	F11	F12	F13	F14
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
2	03.45±1.23	05.47±1.26	06.82±1.8=25	06.29±1.16	11.18±2.09	10.26±1.56	08.36±1.48
4	13.95±1.96	15.01±0.21	17.89±1.46	19.77±2.29	28.77±0.52	26.15±0.26	22.08±1.28
6	22.09±1.44	26.58±0.45	27.35±1.74	31.79±1.11	40.54±1.18	38.18±0.52	35.89±2.28
8	30.72±174	32.38±1.78	35.67±1.78	40.58±0.75	53.58±2.22	52.81±0.58	49.87±2.23
12	44.77±1.75	46.87±1.89	49.97±1.18	58.70±0.56	66.28±2.29	63.49±1.89	60.97±1.16
16	50.36±1.86	53.89±1.16	56.89±1.85	67.09±1.86	79.54±2.85	79.57±1.75	69.76±1.78
20	61.23±1.22	63.28±1.89	65.78±2.18	75.79±2.22	88.78±1.86	87.21±1.24	78.69±0.18
24	77.86±1.86	81.49±0.88	83.73±2.21	84.79±0.85	95.78±1.74	93.23±1.66	91.68±0.89

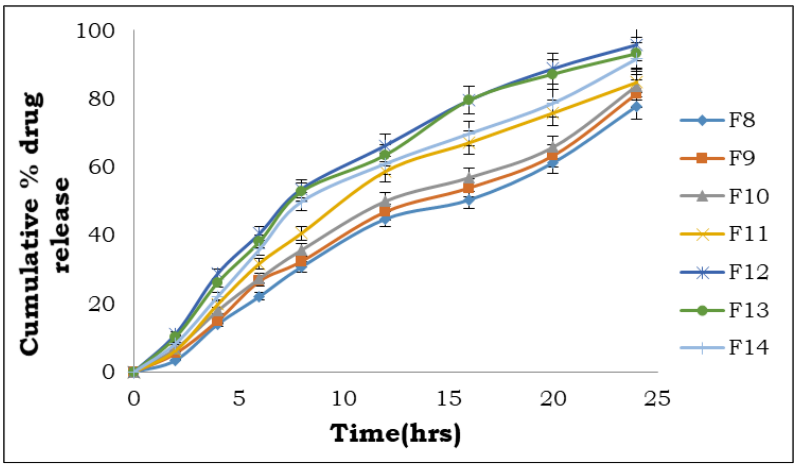

Figure 2 *In vitro* drug release profile of quetiapine fumarate floating tablets F8-F14 in 0.1N Hcl

Table 6 *In vitro* Drug Release Profile of Quetiapine Fumarate floating tablets F15-F21in 0.1N Hcl

Time(h)	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
2	04.18±2.09	05.24±1.16	07.58±1.25	08.47±1.18	17.46±1.25	08.33±1.37	07.55±2.33
4	11.77±0.52	14.04±2.22	16.35±1.14	20.05±1.14	22.34±1.78	18.46±2.24	15.12±3.21
6	32.54±1.18	40.05±1.17	44.64±1.86	46.30±1.98	48.78±1.28	40.97±2.22	38.34±2.289
8	41.58±2.22	48.06±1.82	53.56±1.89	56.40±1.82	59.78±1.24	47.67±1.75	43.12±2.41
12	53.28±2.29	59.94±1.96	62.78±1.75	66.50±1.78	67.66±1.75	63.89±1.96	59.72±2.11
16	61.54±2.85	65.88±1.48	69.69±1.44	71.76±1.44	73.56±1.22	69.67±1.18	65.45±2.75
20	73.78±1.86	75.74±1.47	79.89±2.45	81.27±0.47	84.65±1.16	80.78±2.28	80.56±1.78
24	82.78±1.74	85.87±1.14	89.65±0.85	93.43±0.32	98.65±1.29	94.78±2.23	91.45±1.11

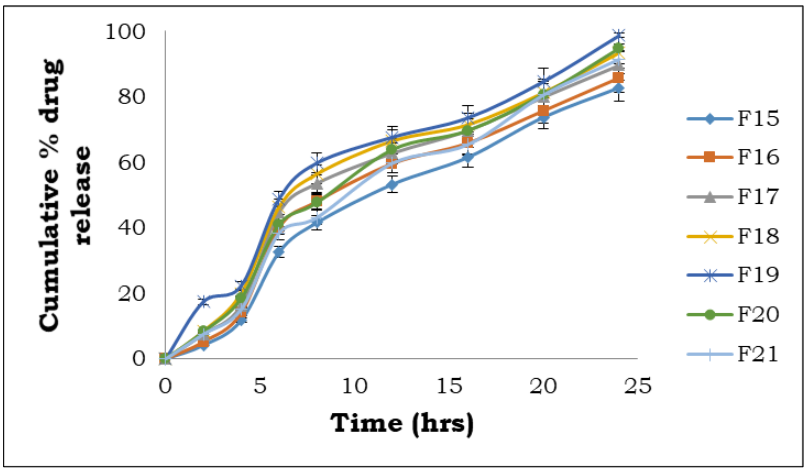

Figure 3 *In vitro* drug release profile of quetiapine fumarate floating tablets F15-F21 in 0.1N Hcl *In vitro* drug release studies

The polymer HPMC K250 PH PRM has controlling effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F1, F2, F3, **F4**, F5, F6 and F7 was 76.34, 79.21, 86.29, **94.34**, 91.34, 88.48 and 86.88 in 24 h respectively. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. The concentrations of polymers were added as increase order to check its drug retarding and release ability upto F4 the release was increased beyond that it shown decrease release so formulation F4 was considered as best formulation among all the seven formulations as it showed good buoyancy properties (floating lag time: 59 sec & floating time >24 hrs) and controlled the drug release for desired period of time (24 hrs).

The polymer HPMC K750 PH PRM has controlling effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F8, F9, F10, F11, **F12**, F13 and F14 was 77.86, 81.49, 83.73, 84.79, **95.78**, 93.23and 91.68 in 24 h respectively. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. The concentrations of polymers were added as increase order to check its drug retarding and release ability upto F12 the release was increased beyond that it shown decrease release so formulation F12 was considered as best formulation among all the seven formulations as it showed good buoyancy properties (floating lag time: 37 sec & floating time >24 hrs) and controlled the drug release for desired period of time (24 hrs).

The polymer HPMC K 1500 PH PRM has controlling effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F15, F16, F17, F18, **F19**, F20 and F21 was 82.78, 85.87, 89.65, 93.43, **98.65**, 94.78 and 91.45 in 24 h respectively. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. The concentrations of polymers were added as increase order to check its drug retarding and release ability upto F19 the release was increased beyond that it shown decrease release so formulation F19 was considered as best formulation among all the seven formulations as it showed good buoyancy properties (floating lag time: 31 sec & floating time >24 hrs and controlled the drug release for desired period of time (24 hrs).

An *In vitro* release profile of Quetiapine Fumarate was sequentially determined in gastric fluid of pH 1.2.

3.2. *In vitro* drug release studies in hydroalcoholic dissolution media

In vitro drug release in hydroalcoholic dissolution media was performed for optimized formulations of F4, F12 and F19 to investigate the ethanol vulnerability on dose dumping.

Table 7 *In vitro* % Drug release in Presence of different v/v of Ethanol and 0.1N Hcl for HPMC K250 PH PRM

Time (h)	F4	10%	20%	30%	40%
0	0	0	0	0	0
2	9.24±0.12	11.67±0.58	14.47±1.30	14.56±0.86	15.23±1.85
4	26.95±0.95	28.19±0.91	30.2±2.03	31.03±1.28	34.06±0.94
6	40.09±0.84	41.16±0.81	43.13±1.22	43.45±1.6	45.23±0.65
8	50.72±1.02	51.18±0.93	53.15±1.20	54.65±1.43	56.25±1.28
12	61.77±1.37	65.9±1.44	68.67±1.05	69.23±1.28	70.2±1.97
16	72.36±1.82	73.67±1.36	75.7±1.99	77.35±1.96	78.21±1.86
20	83.23±0.95	85.6±1.28	88.67±1.04	89±1.88	89.82±1.45
24	94.34±1.56	94.75±0.98	95.23±1.23	97.01±1.34	98.09±1.29

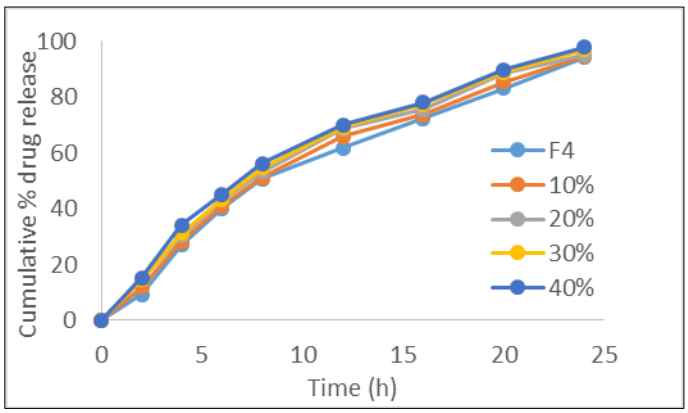

Figure 4 % Drug release in Presence of different v/v of Ethanol and 0.1N Hcl for HPMC K250

Table 8 *In vitro* % Drug release in Presence of different v/v of Ethanol and 0.1N Hcl for HPMC K750 PH PRM

Time(h)	F12	10%	20%	30%	40%
0	0	0	0	0	0
2	11.18±1.08	11.95±1.87	12.03±0.96	13.5±0.96	16±0.86
4	28.77±1.75	28.96±1.44	30.5±1.23	32.3±1.02	34.2±1.33
6	40.54±1.67	42.05±1.85	42.36±1.52	44.21±1.23	46.8± 1.42
8	53.58±1.44	54.06±1.56	55.03±1.48	56.85±1.45	58.041.87±
12	66.28±1.49	67.5±1.01	68.01±1.06	68.75±1.36	70.05±1.68
16	79.54±1.38	79.95±1.46	80.12±1.15	81.2±1.53	84± 1.55
20	88.78±1.65	89.03±0.98	90.04±1.24	91.0±1.88	91.95±1.34
24	97.78±0.86	96.01±0.46	96.4±1.31	97.25±1.64	98.95±2.01

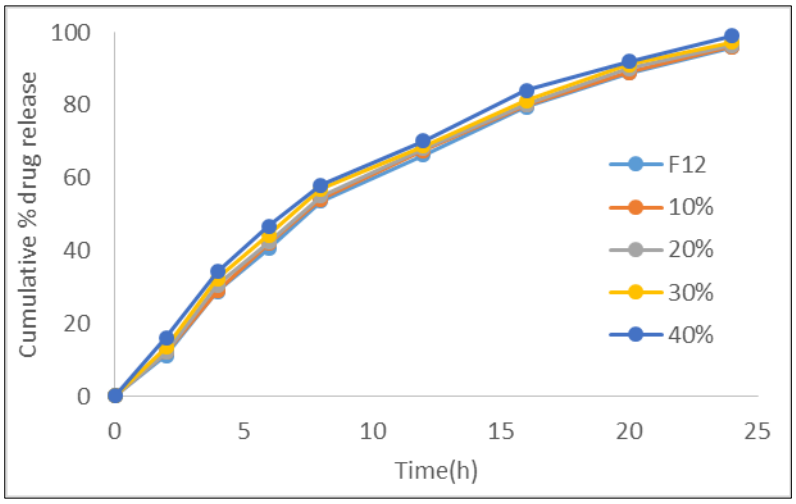

Figure 5 % Drug release in Presence of different v/v of Ethanol and 0.1N Hcl for HPMC K750

Table 9 *In vitro* % Drug release in Presence of different v/v of Ethanol and 0.1N Hcl for HPMC K1500 PH PRM

Time (h)	F19	10%	20%	30%	40%
0	0	0	0	0	0
2	17.46±1.22	18.64±0.74	19.62±1.34	20.36±0.74	20.58±1.07
4	22.34±1.30	23.44±0.69	25.32±1.95	26.54±1.22	28.32±1.58
6	48.78±1.23	48.96±0.85	49.12±1.46	50.31±1.48	52.08±1.34
8	59.78±1.54	60.1±1.98	61.2±1.82	62.05±1.94	64.28±2.20
12	67.66±1.47	68.23±1.66	69.42±1.62	70.2±1.57	71.5±1.08
16	73.56±1.95	74.25±1.73	75.21±1.54	76.25±1.72	78.41±1.5
20	84.65±1.64	85.64±1.42	86.2±1.21	91.0±1.84	92.35±1.27
24	98.65±2.21	99.0±1.57	99.5±0.96	99.32±1.33	99.98±1.20

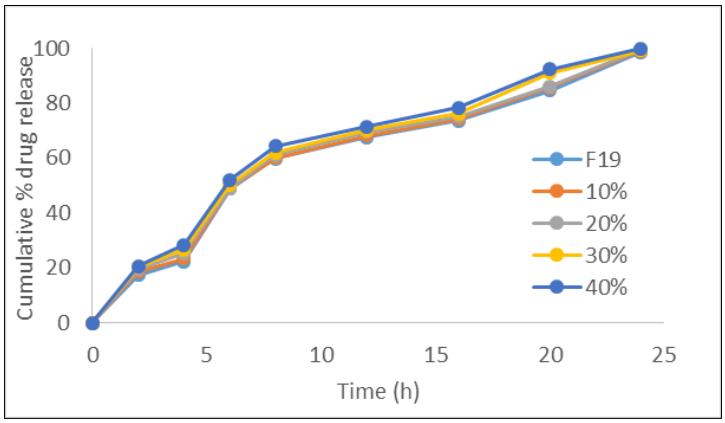

Figure 6 % Drug release in Presence of different v/v of Ethanol and 0.1N Hcl for HPMC K1500

F4, F12 and F19 formulations retained their hydrated structural integrity when exposed to 10%, 20%, 30% and 40% v/v ethanol solutions for up to 24 hours without in dose-dumping

3.3. Drug -excipient compatibility studies

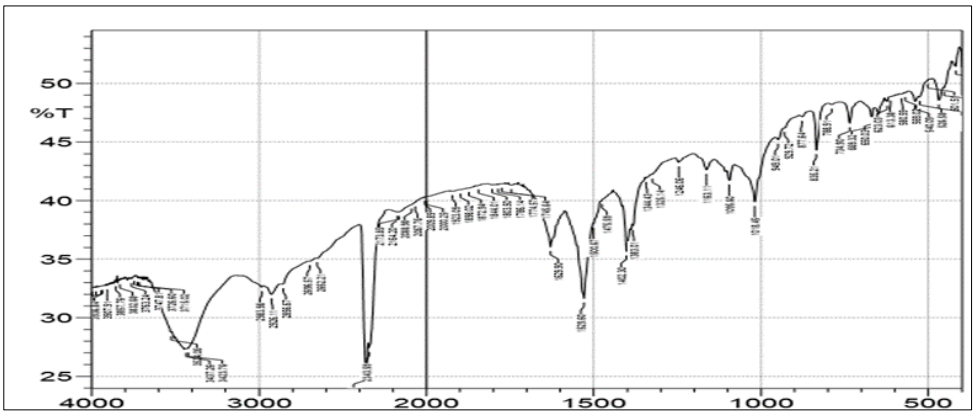

Figure 7 FTIR spectrum Quetiapine fumarate pure drug

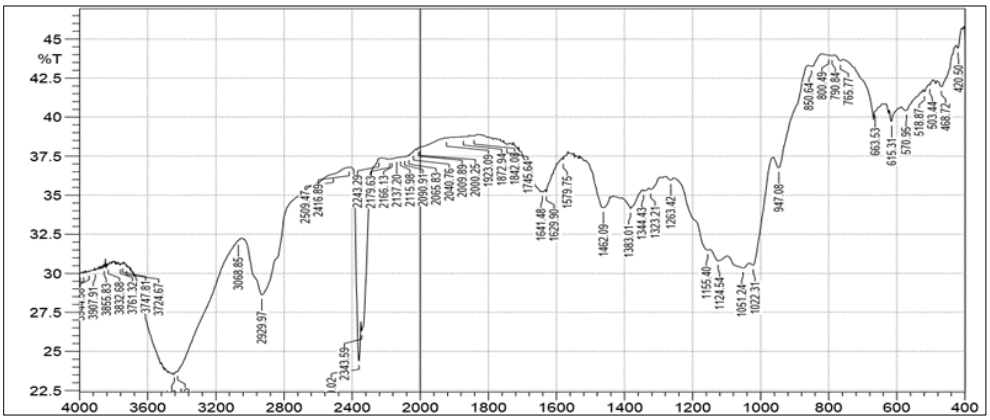

Figure 8 FTIR spectrum of HPMC K1500 PH PRM

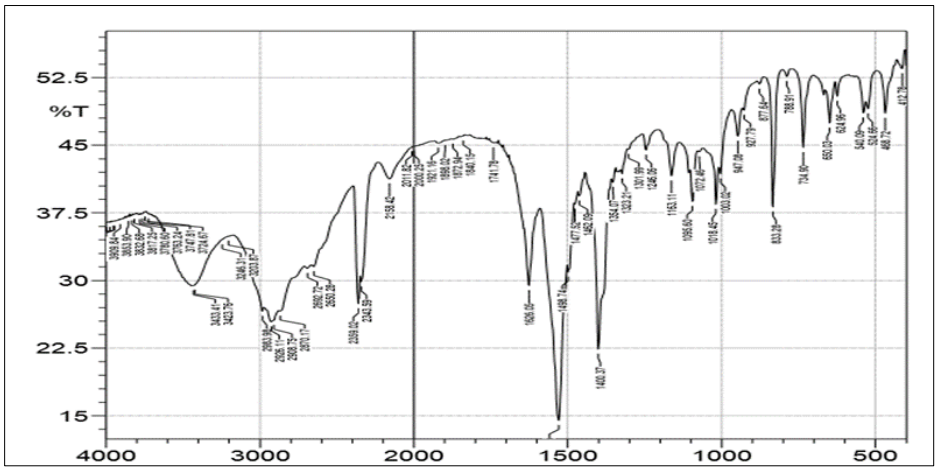

Figure 9 FTIR spectrum of Quetiapine fumarate formulation (F19)

FTIR spectra of optimized formulation showed both characteristics peaks of drug and polymer indicating no drug-polymer interaction.

4. Conclusion

Quetiapine fumarate used for the treatment of schizophrenia. Quetiapine Fumarate, highly soluble in acidic pH but poorly soluble in alkaline pH and suitable for gastro retentive drug delivery system. In the present study different polymers like HPMC K 250 PH PRM, HPMC K 750 PH PRM and HPMC K 1500 PH PRM were used to prepare Floating tablet of quetiapine fumarate. Drug and polymers were subjected for compatibility study using FT-IR which suggest there was no interaction between drug and polymer. Twenty one formulations (F1-F21) were prepared by direct compression method using different polymers such as HPMC K 250 PH PRM, HPMC K 750 PH PRM and HPMC K 1500 PH PRM. Seven formulations were made using various concentrations of each polymer. All the above polymers are innovative and effective in retarding the drug release.

The effervescent agents i.e. sodium bicarbonate and citric acid were used in increase order of their concentrations but floating lag time is not directly proportional to its concentrations. Thus, gastric floating tablets were formulated by varying proportions of polymers by direct compression method and they were evaluated. All the physico-chemical properties of the formulations were within the limit. The formulations from each polymer F4, F12 and F19 gave better controlled drug release and floating properties in comparison to the other formulations.

F4, F12 and F19 formulations retained their hydrated structural integrity when exposed to 10%, 20%, 30% and 40% v/v ethanol solutions for up to 24 hours without in dose-dumping. The inherent hydroalcohol solubility properties these polymers guards against any potential dose dumping. The concern around alcohol dose dumping seems negligible for these polymers.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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