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DESIGN AND EVALUATION OF AMOXICILIN TRIHYDRATE FLOATING GRANULES PREPARED BY MELT GRANULATION TECHNIQUE

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Keywords:

Water soluble drugs, Floating granules, Lipid carriers, Zero order release

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ABSTRACT: The purpose of this study was to design and evaluate Amoxicillin trihydrate floating granules by melt granulation technique using Gelucire 43/01 and Campritol 888 ATO as lipid carriers. Polymers HPMC K4M and Ethyl Cellulose as release rate modifiers. The granules were evaluated by FTIR studies, differential scanning calorimetry, Scanning Electron microscopy, drug content, *in vitro* floating ability and *in vitro* drug release. The optimized formulation showed good floating ability and 98% drug was released in 12 h with both lipid carriers. The drug release from optimized formulations F3 and F9 followed zero order patterns and governed by Non-Fickian mechanism which was confirmed by the 'n' values of Koresmeyer Peppas equations. Formulations of Gelucire 43/01 had shown superior retardation and floating characteristics compared to that of Campritol 888 ATO. In conclusion, hydrophobic lipid, Gelucire 43/01 can be considered as an effective carrier for design of a multiunit floating drug delivery system of highly water - soluble drugs such as Amoxicillin trihydrate.

INTRODUCTION: The Oral route currently represents the most predominant and preferable route of drug delivery. Oral drug delivery systems have progressed from conventional immediate release to site-specific delivery over a period of time. The single-unit systems such as tablets and capsules which exhibit all or none emptying phenomena can be overcome by the design of multi-unit systems such as pellets and granules which may be more suitable because they claim to reduce the inter-subject variability in absorption and lower the probability of dose dumping [2]. Floating drug delivery systems were first discovered by Davis in 1968.

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These systems prolong the gastric residence time and remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents [8]. These floating granules were prepared by melt granulation technique which is less time consuming; enhance the solubility and dissolution rate of poorly water soluble drugs [6]. Amoxicillin is a semi-synthetic β-lactum antibiotic effective against Helicobacter pylori infections.

Amoxicillin trihydrate is considered as a good candidate for incorporation in a gastro-retentive dosage form due to its high solubility in stomach pH than in the small intestine pH. Lipid excipients like Gelucires, Campritol 888 ATO, Chitin are used in the preparation of sustained release formulations. HPMC K4M is used as swellable polymer which forms a gel layer over the drug for controlled release. Ethyl cellulose is another polymer used which retards the disintegration and also dissolution.

A possible interaction between drug and polymers was also investigated by Fourier Transform Infrared Spectroscopy (FTIR) and differential scanning calorimetry (DSC) study. The objective of this study is to formulate Amoxicillin trihydrate (AT) multi unit floating granules by using lipid excipients and release rate modifiers and was evaluated using DSC, FTIR and for *in vitro* drug release characteristics.

MATERIALS: Amoxicillin trihydrate was supplied by Nestor Pharmaceuticals Pvt. Ltd., Lipid carriers Gelucire 43/01 and Campritol 888 ATO were Generous gift from Gattefosse (St. Priest, Cedex, France) and polymers HPMC K4M and Ethyl Cellulose were supplied by Colorocn Asia Pvt. Ltd., and solvents used were of analytical grade.

METHODS:

Preparation of Calibration Curve of Amoxicillin Trihydrate: Solutions ranging from 20- 240 µg/ml were prepared by using 0.1N HCl and absorbance was measured at λ_{max} of 272 nm using UV-Visible spectrophotometer (Elico, SL - 159, India) against 0.1N HCl as blank **Table 1**, **Fig. 1**.

Solubility of Amoxicillin Trihydrate: Excess samples were placed in 0.1N HCl, pH 6.8 phosphate buffer and water and placed on horizontal shaker for 24 hr at 37 °C. The supernatant was filtered and the filtrate was diluted with respective solvents. Then values were observed using UV - Visible spectrophotometer (Elico, SL - 159, India) at λ_{max} of 272 nm **Table 2**.

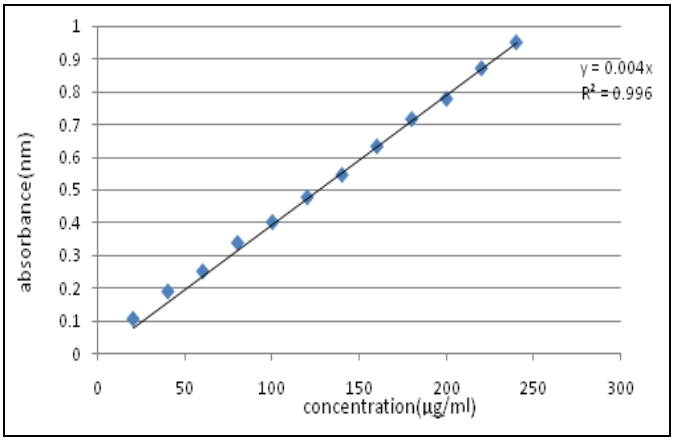


FIG. 1: CALIBRATION CURVE OF AT IN 0.1 N HCl AT λ_{max} 272 nm

Drug - excipient Compatibility Studies:

Fourier Transform Infrared (FT - IR) Spectroscopy: The FTIR spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer, FT - I Insf, USA) by KBr method. Pure AT, individual polymers, physical mixtures and optimized formulations were subjected to FTIR study. Samples were mixed with dry crystalline KBr in a 1:100 (sample: KBr) ratio and pellets were prepared. The spectrum of samples was obtained within the wave number region from 3500 to 700 cm^{-1} **Fig. 2.**

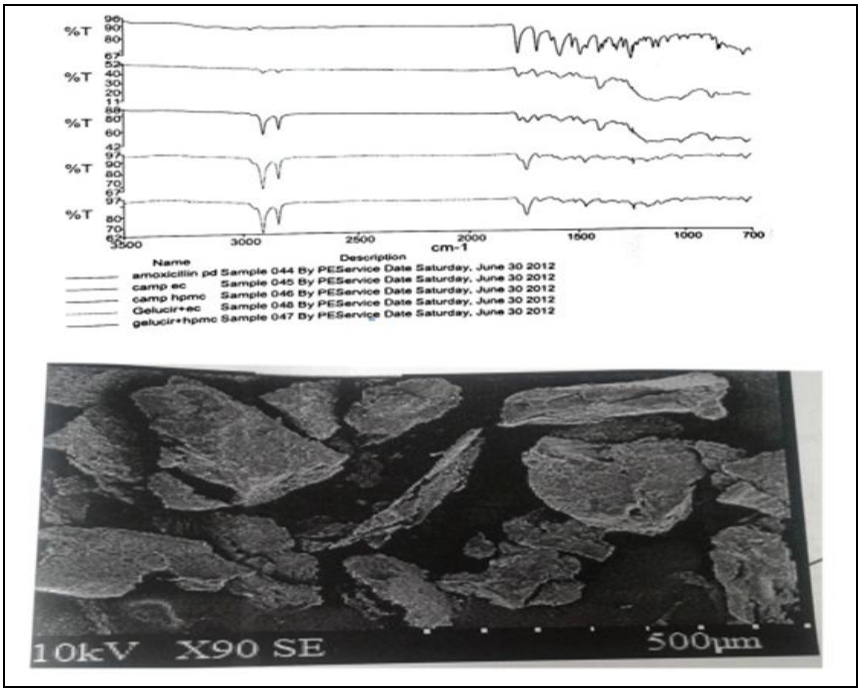
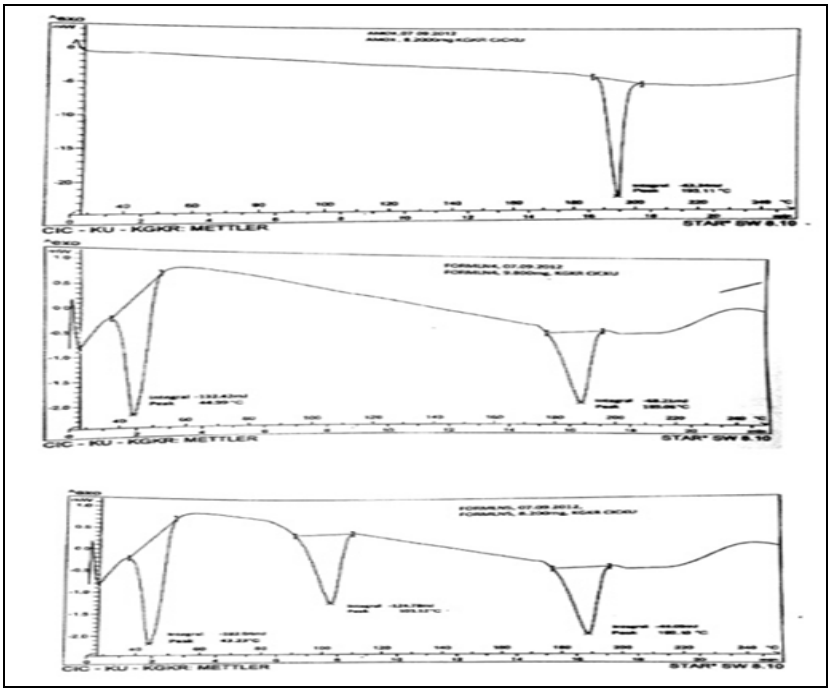
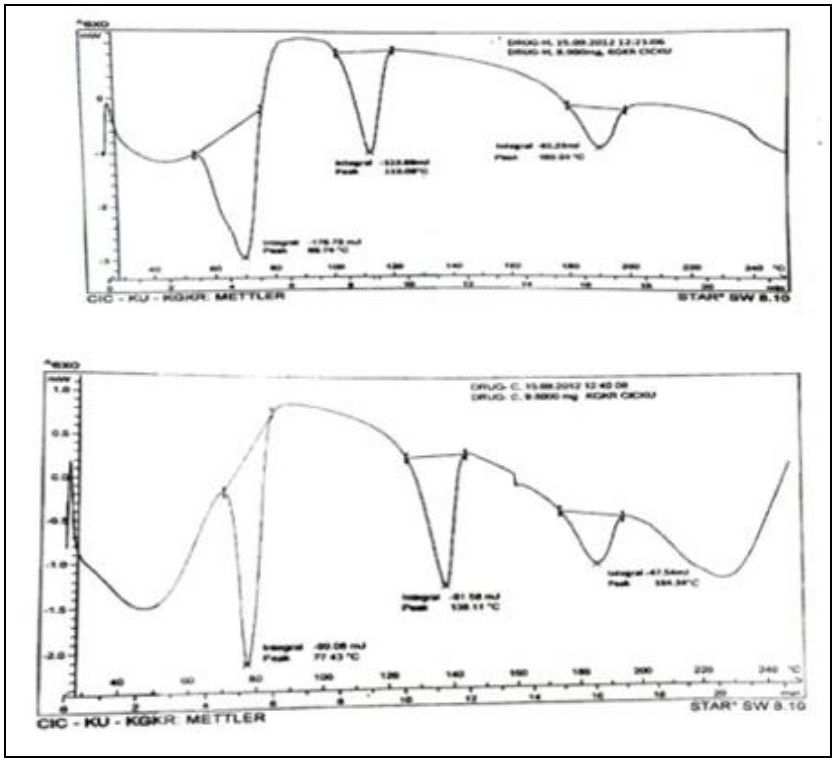


FIG. 2: FOURIER TRANSFORM (FT - IR) INFRARED SPECTROSCOPY AND SEM

Differential Scanning Calorimetry (DSC): DSC experiments were carried out to find the presence of any interaction between the drug and excipients (Agarwal A. M. *et al*., 2003). 5 - 15 mg of samples were pierced in DSC aluminium pan and scanned in the temperature range of 50 - 250 °C. The heating rate was 10 °C / min. Liquid nitrogen served as purged gas. Indium is used as reference. The differential thermal analyser (DSC 822e/200, Mettler Toledo, Switzerland) was used for this purpose **Fig. 3**.



1, 2 AND 3 (FROM TOP TO BOTTOM)



4 AND 5 (FROM TOP TO BOTTOM)

FIG. 2: 1) DSC OF PURE DRUG – AT, 2) DSC OF AT, GELUCIRE 43/01 AND HPMC K4M, 3) DSC OF AT, GELUCIRE 43/01 AND ETHYL CELLULOSE, 4) DSC OF AT, CAMPRITOL 888 ATO AND HPMC K4M, 5) DSC OF AT, CAMPRITOL 888 ATO AND ETHYL CELLULOSE

Formulation Development:

Preparation of AT floating Granules by Melt Granulation Technique: Floating granules containing AT, lipids of various ratios (drug; lipid: 1:1, 1:1.25 and 1:1.5) prepared by using melt granulation technique. The polymers added were HPMC K4M, 0.5 parts and ethyl cellulose, 0.1 and 0.2 parts to the optimized formulation.

Lipids, Gelucire 43/01 and Campritol 888 ATO were melted separately at 50 °C and 74 °C respectively, to which drug and drug additive mixture was added, mixed well and cooled to RT. The mass was then passed through 850 µm sieve to obtain uniform sized granules [7] **Table 3** and **4**.

Evaluation of Granules:

***In vitro* Buoyancy Study:** The in *vitro* buoyancy was characterized by floating lag time and total floating time **Table 5**. The test was performed using USP 24 type II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India) by placing 500 mg granules in 900 ml of simulated gastric fluid pH 1.2 at 100 rpm at 37 ± 0.5 °C temperature. The time required for the granules to rise to the surface of the dissolution medium and the duration of time the granules constantly floated on the dissolution medium were noted as floating lag time and total floating time respectively [5].

Drug Content and Percentage Yield: 10 mg of granules were added to 10 ml of distilled water, heated to 60 °C to 70 °C, and allowed to cool to room temperature. The lipid was solidified and the drug solution was filtered through Whatman No.1 paper. The filtrate samples were analyzed for drug content using UV spectrometry (Elico, SL-159, India) at 272 nm after suitable dilutions. Drug stability in the dissolution medium and distilled water was checked for a period of 8 hrs. Determinations were performed in triplicate. Percentage yield of each formulation was calculated **Table 6**.

Scanning Electron Microscopy: SEM studies were performed for the optimized formulation to determine the surface morphology of floating granules. The magnification of the technique was X90 (**Fig. 3** it's already mentioned above).

***In vitro* Dissolution Studies:** The dissolution test was performed using 900 ml of 0.1N HCl at 37 ± 0.5 °C and 50 rpm using USP Type II dissolution apparatus. At predetermined time intervals samples (5 ml) were collected and replaced with same volume of fresh media. The absorbances of these solutions were estimated using UV-Visible spectrophotometer at λ_{max} of 272 nm[3] **Table 7**, **8**, **9**, **10** and **Fig. 4** and **5**.

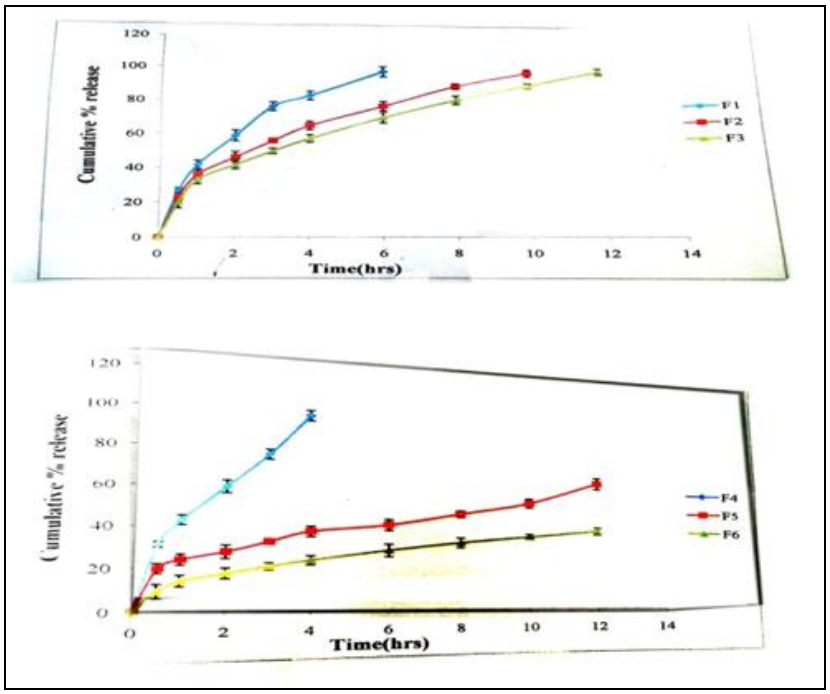


FIG. 4: 1) CUMULATIVE % DRUG RELEASE OF FORMULATIONS WITH GELUCIRE 43/01, CUMULATIVE PERCENTAGE DRUG RELEASE PROFILES OF FORMULATIONS WITH GELUCIRE 43/01, PMC K4M (F4) AND GELUCIRE 43/01, ETHYL CELLULOSE (F5 AND F6)

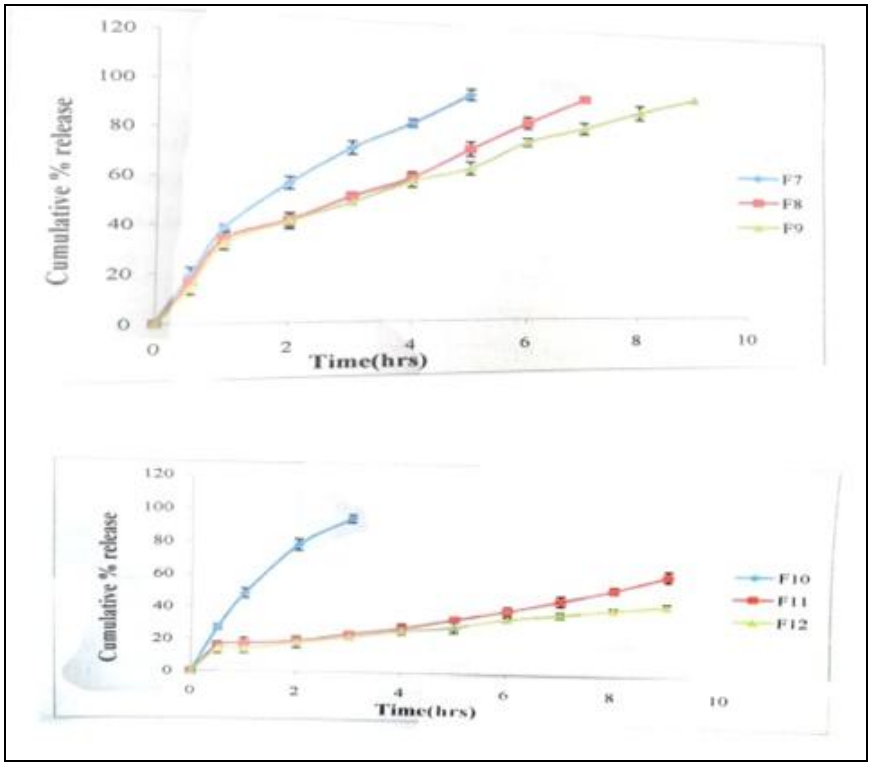


FIG. 5: 1) CUMULATIVE % DRUG RELEASE OF FORMULATIONS WITH CAMPRITOL 888 ATO, 2) CUMULATIVE PERCENTAGE DRUG RELEASE PROFILES OF FORMULATIONS WITH CAMPRITOL 888 ATO, HPMC K4M (F10) AND CAMPRITOL 888 ATO, ETHYL CELLULOSE (F11 AND F12)

Mathematical Modelling of Release Profiles: In order to establish the mechanism of drug release from the granules, the experimental data was fitted to different kinetic models. The drug release data was subjected to various mathematical kinetic models like zero order, first order, Higuchi's model and Korsmeyer's model, when the release mechanism is not well known or when more than one type of release phenomena could be involved. The 'n' value could be used to characterize different release mechanisms [4] **Table 11**.

RESULTS AND DISCUSSION:

TABLE 1: CALIBRATION CURVE OF AT IN 0.1 N HCl AT λ_{max} 272 nm

Concentration (µg/ml)	Absorbance (nm)
20	0.106
40	0.190
60	0.251
80	0.338
100	0.401
120	0.477
140	0.545
160	0.632
180	0.715
200	0.777
220	0.87
240	0.949

TABLE 2: SOLUBILITY STUDY DATA OF AT

Medium	Solubility (mg/ml)
0.1 HCl	139.1
pH 6.8 phosphate buffer	4.7
Water	3.9

Formulation Trials:

TABLE 3: AT - GELUCIRE 43/01 FLOATING GRANULES CONTAINING HPMC K4M AND ETHYL CELLULOSE

Ingredients	Formulations (mg)					
	F1	F2	F3	F4	F5	F6
AT	100	100	100	100	100	100
Gelucire 43/01	100	125	150	150	150	150
HPMC K4M	-	-	-	50	-	-
Ethyl Cellulose	-	-	-	-	10	20

TABLE 4: AT - CAMPRITOL 888/ATO FLOATING GRANULES CONTAINING HPMC K4M AND ETHYL CELLULOSE

Ingredients	Formulations (mg)					
	F1	F2	F3	F4	F5	F6
AT	100	100	100	100	100	100
Campritol 888/ATO	100	125	150	150	150	150
HPMC K4M	-	-	-	50	-	-
Ethyl Cellulose	-	-	-	-	10	20

Evaluation of Granules:

TABLE 5*: IN VITRO* BUOYANCY STUDY

Formulation code	Floating Lag time (sec)	Total floating time (hrs) of Gelucire 43/01	Total floating time (hrs) of Campritol 888 ATO
F1	0	>12	10
F2	0	>12	10
F3	0	>12	10
F4	0	>12	10
F5	0	>12	10
F6	0	>12	10
F7	0	>12	10
F8	0	>12	10
F9	0	>12	10
F10	0	>12	10
F11	0	>12	10
F12	0	>12	10

TABLE 6: DRUG CONTENT AND PERCENTAGE YIELD

Formulation code	Drug content in 10 mg of granules	Percentage yield (%)
F1	94	91.50
F2	96	91.20
F3	98	91.00
F4	93	93.43
F5	95	94.01
F6	94	94.23
F7	94	90.29
F8	93	90.47
F9	97	90.55
F10	93	94.26
F11	94	94.31
F12	95	94.55

Scanning Electron Microscopy: SEM of optimized formulation F3 which contains Gelucire 43/01 as carrier. The magnification o the technique was X90. The size of the granules was found to be 500 µm.

In vitro Dissolution Studies:

TABLE 7: CUMULATIVE % DRUG RELEASE OF FORMULATIONS WITH GELUCIRE 43/01

Time points (hrs)	Cumulative % drug release		
	F1	F2	F3
0	0	0	0
0.5	28.68±1.3	22.74±2.3	19.87±3.3
1	42.79±2.3	35.97±2.6	35.66±2.7
2	56.71±3.2	46.09±3.2	42.63±2.5
3	71.34±2.5	55.64±1.3	49.58±1.7
4	82.59±2.6	64.63±2.6	56.99±2.2
6	98.52±3.1	76.44±2.8	67.53±3.2
8		88.80±1.7	79.86±2.6
10		97.35±2.4	90.22±1.4
12			98.59±1.8

F3 was considered as best formulation among three formulations as it showed good *in vitro* buoyancy properties and sustained drug release upto 12hrs

TABLE 8: CUMULATIVE PERCENTAGE DRUG RELEASE PROFILES OF FORMULATIONS WITH GELUCIRE 43/01, PMC K4M (F4) AND GELUCIRE 43/01, ETHYL CELLULOSE (F5 AND F6)

Time points (hrs)	Cumulative % drug release		
	F4	F5	F6
0	0	0	0
0.5	31.28±1.6	19.94±2.3	9.23±2.7
1	43.02±2.8	24.08±3.2	14.10±2.5
2	59.66±3.3	27.93±2.6	17.75±3.3
3	76.37±2.4	33.08±1.3	21.16±1.7
4	97.09±2.5	38.43±2.8	24.32±2.2
6		42.56±1.4	29.67±3.2
8		49.43±2.4	34.29±1.3
10		56.46±3.1	38.18±1.8
12		68.44±2.1	42.08±1.4

The difference in drug release profiles of above three formulations was due to the presence of different concentrations of polymers

TABLE 9: CUMULATIVE % DRUG RELEASE OF FORMULATIONS WITH CAMPRITOL 888 ATO

Time points (hrs)	Cumulative % drug release		
	F7	F8	F9
0	0	0	0
0.5	19.41±3.2	17.94±1.3	14.87±2.3
1	38.80±1.3	32.38±1.6	32.29±2.0
2	57.71±2.6	42.43±2.8	41.76±1.3
3	73.13±2.8	52.64±1.7	50.11±3.2
4	84.58±1.7	61.24±2.2	59.58±1.6
6	98.01±2.4	74.13±3.2	66.71±2.8
8		86.48±1.5	77.96±1.9
10		97.77±0.6	92.44±2.4
12			99.12±0.7

F9 was considered as best formulation among three formulations as it showed good *in vitro* buoyancy properties and sustained drug release upto 12 hrs

TABLE 10: CUMULATIVE PERCENTAGE DRUG RELEASE PROFILES OF FORMULATIONS WITH CAMPRITOL 888 ATO, HPMC K4M (F10) AND CAMPRITOL 888 ATO, ETHYL CELLULOSE (F11 AND F12)

Time points (hrs)	Cumulative % drug release		
	F10	F11	F12
0	0	0	0
0.5	27.03±2.7	15.74±1.6	13.86±1.3
1	48.32±2.5	17.56±2.6	14.01±2.8
2	78.43±1.7	19.21±1.7	18.24±1.17
3	94.46±3.2	23.83±2.2	21.84±3.1
4		27.72±1.5	26.02±2.3

6	33.56±3.3	28.70±1.4
8	39.16±2.6	34.05±3.2
10	45.68±3.2	36.97±1.2
12	61.54±1.5	43.12±2.6

The difference in drug release profiles of above three formulations was due to the presence of different concentrations of polymers

TABLE 11: MATHEMATICAL MODELING OF RELEASE PROFILES

Formulation code	R^2 value				Release exponent
	Zero order	First order	Higuchi	Korsmeyer-Peppas	'n' value
F1	0.9526	0.9384	0.9970	0.9983	0.467
F2	0.9826	0.9269	0.9988	0.9966	0.887
F3	0.9942	0.8492	0.9910	0.9817	0.453
F4	0.9607	0.8729	0.9811	0.9926	0.662
F5	0.9590	0.8667	0.9908	0.9880	0.591
F6	0.9790	0.9047	0.9991	0.9881	0.425
F7	0.9581	0.5933	0.9825	0.9655	0.735
F8	0.9943	0.9931	0.9593	0.9592	0.542
F9	0.9969	0.9648	0.9846	0.9833	0.524
F10	0.9823	0.8588	0.9921	0.9830	0.659
F11	0.9968	0.9472	0.9896	0.9947	0.669
F12	0.9974	0.9379	0.9642	0.9922	0.991

Regression coefficient (R^2) value of optimized formulations F3 and F9 are 0.9942 and 0.9969 respectively. By this it is confirmed that both optimized formulations followed zero order release, governed by non-fickian mechanism by observing their release exponent 'n' values

CONCLUSION: The present study showed that there is no incompatibility between Amoxicillin trihydrate, lipids (Gelucire 43/01 and Campritol 888 ATO) and various polymers by performing FT-IR and DSC studies. Formulations F3 and F9 showed better controlled release and floating properties I comparison to other formulations.

The drug release showed zero order patterns for F3 and F9 and the release pattern was governed by non-fickian mechanism which was confirmed by release exponent 'n' values. Thus, formulations with Gelucire 43/01 showed superior release and floating properties than the formulations with Campritol 888 ATO. Thus, Gelucire 43/01 can be a good carrier for a multi unit floating drug delivery systems.

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CONFLICT OF INTEREST: Nil

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