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

Dr Mohamed Mutahar RK[1], Dr S. Satyanandam[2], Mrs.Anitha Surakala[3]

Professor[1], Associate professor[2]. Assistant professor[3]

Department of Pharmaceutics,

Global College of Pharmacy, Hyderabad. Chilkur (V), Moinabad (M), Telangana- 501504

ABSTRACT: This research set out to create and assess Amoxicillin trihydrate floating granules utilizing the melt granulation process and the lipid carriers Gellucire 43/01 and Campritol 888 ATO. Rubbers High-Performance MC To modify the rate of release, K4M and Ethyl Cellulose are used. A variety of methods were used to assess the granules, including Fourier transform infrared spectroscopy, scanning electron microscopy, drug content, floating ability in vitro, and drug release in vitro. With both lipid carriers, the improved formulation exhibited excellent floating ability and drug release in 12 hours. The 'n' values of Korsmeyer-Peppas equations revealed that the drug release from improved formulations F3 and F9 followed zero-order patterns and was driven by a non-Fickian mechanism. Gelucire 43/01 formulations outperformed Campritol 888 ATO in terms of retardation and floating. In conclusion, Amoxicillin trihydrate and other highly water-soluble medicines may be effectively delivered via a multiunit floating drug delivery system using the hydrophobic lipid Gelucire 43/01.

Keywords: Lipid carriers, floating granules, and pharmaceuticals soluble in water Release of zero orders

INTRODUCTION: Right now, the oral route is where most people want to take their medications. Over time, site-specific administration has replaced traditional immediate release as the preferred method of oral medication delivery. Pellets and granules are examples of multi-unit systems that aim to decrease the likelihood of dose dumping 2 and inter-subject variability in absorption, making them a potential improvement over single-unit systems like tablets and capsules that display all or none emptying phenomena. In 1968, Davis made the first discovery of floating medication delivery devices.

Without influencing the pace of gastric emptying of other contents, these systems increase the duration of gastric residency and stay buoyant in the stomach for a long time. 8. The floating granules were made using the faster melt granulation method. They improve the solubility and rate of dissolution of medications that are not very water soluble. Helicobacter pylori infections may be effectively treated with amoxicillin, a semi-synthetic β-lactum antibiotic.

The increased solubility of amoxicillin trihydrate in the stomach compared to the small intestine makes it a promising option for inclusion into a gastro-retentive dose form. For the purpose of creating sustained-release formulations, lipid excipients such as chitin, gelucires, and campritol 888 ATO are used. A gel layer may be formed over the medicine to allow for controlled release using HPMC K4M, a swellable polymer. Another polymer that slows down dissolving and disintegration is ethyl cellulose.

A research was conducted using Fourier Transform Infrared Spectroscopy (FTIR) and differential scanning calorimetry (DSC) to evaluate the possibility of a drug-polymer interaction. This work aimed to develop multi-unit floating granules of amoxicillin trihydrate (AT) utilizing lipid excipients and release rate modifiers. The development process was assessed using differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and in vitro drug release characteristics.

MATERIALS: The following lipid carriers were generously provided: Gattefosse (St. Priest, Cedex, France), Amoxicillin trihydrate from Nestor Pharmaceuticals Pvt. Ltd., HPMC K4M and Ethyl Cellulose from Colorocn Asia Pvt. Ltd., and analytical grade solvents.

ASSESSMENT STEPS:

Building the Amoxicillin Trihydrate Calibration Curve: 0.1N HCl was used to create solutions with concentrations ranging from 20-240 µg/ml. The absorbance was measured at ƛmax of 272 nm using a UV-Visible spectrophotometer (Elico, SL - 159, India) in comparison to 0.1N HCl, which served as a blank (Table 1, Fig. 1).

The solubility of amoxicillin trihydrate was determined by placing excess samples in a solution of 0.1N HCl, pH 6.8 phosphate buffer, and water. The mixture was then shaken horizontally at 37 °C for 24 hours. Diluting the filtrate, the supernatant was strained. with respective solvents. Then values were observed using UV - Visible spectrophotometer (Elico, SL - 159, India) at λ_{max} of 272 nm **Table 2**.

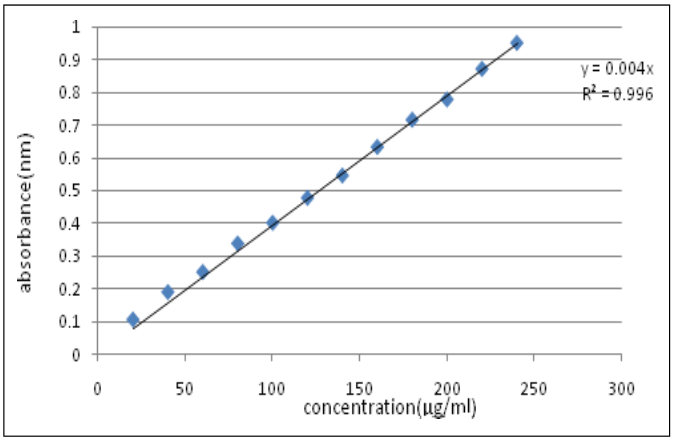


FIG. 1: CALIBRATION CURVE OF AT IN 0.1 N HCl AT λ_{max} 272 nm

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 3500to 700 cm^{-1} **Fig. 2.**

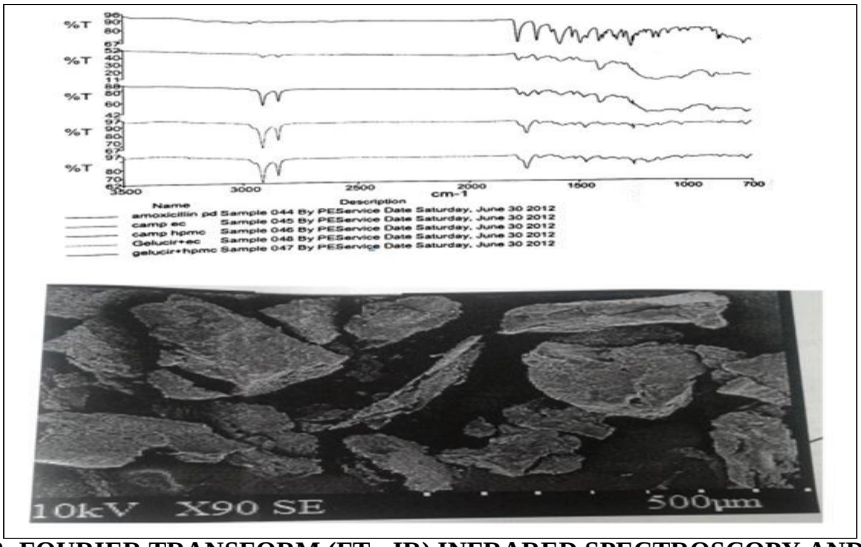
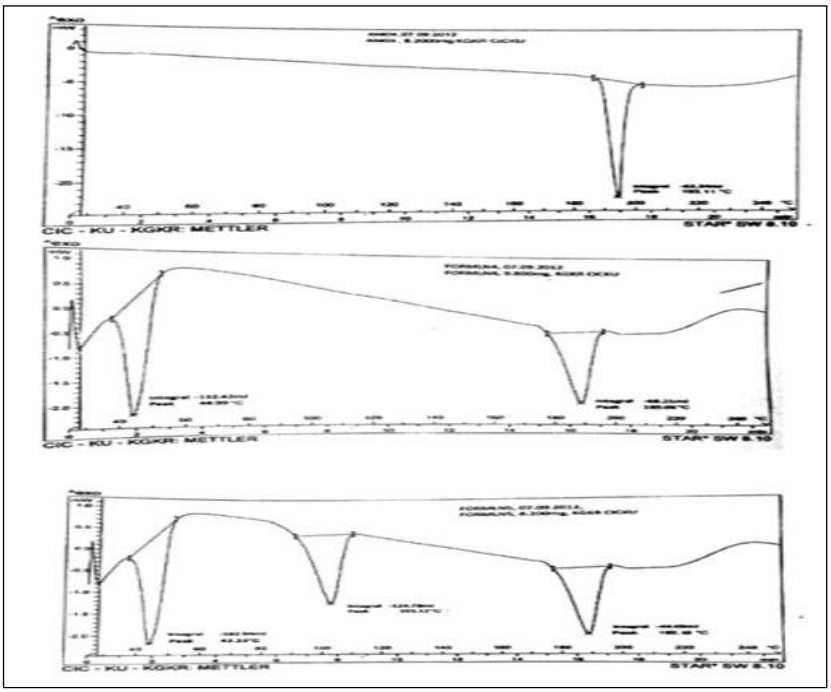
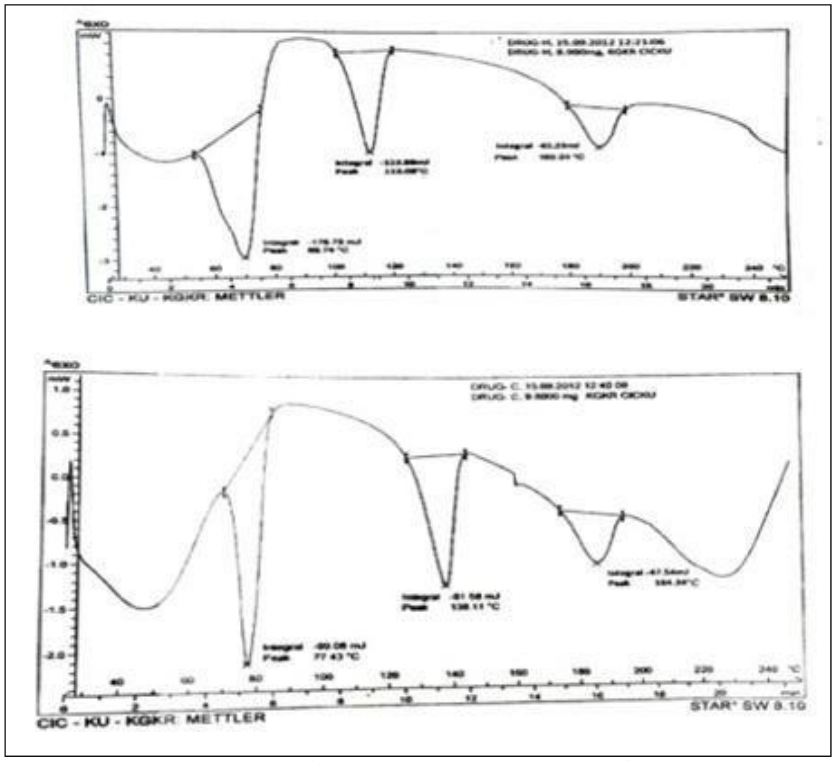


FIG. 2: FOURIER TRANSFORM (FT - IR) INFRARED SPECTROSCOPY AND SEM

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 scannedin 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 studieswere 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 ± °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**.

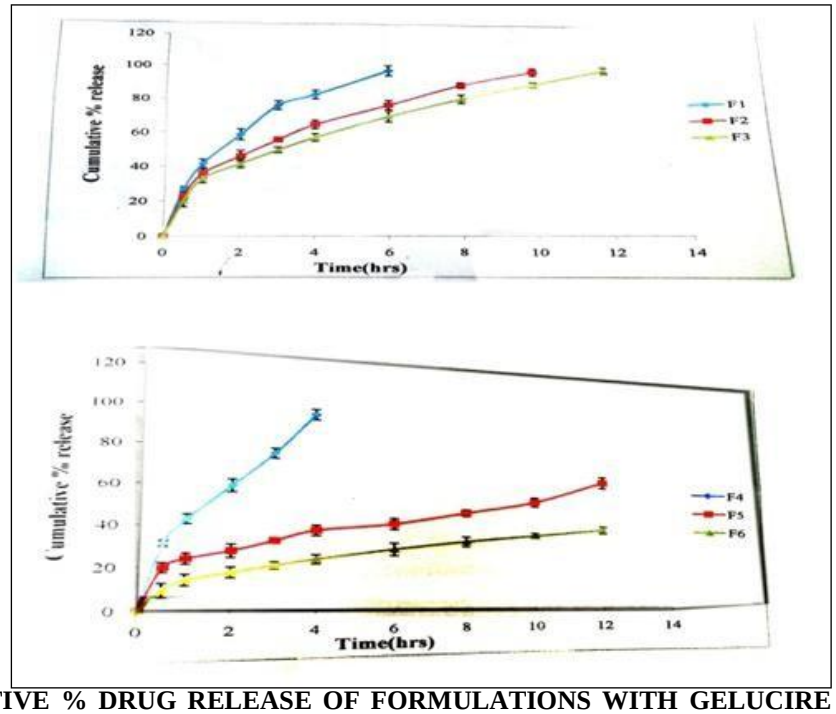


FIG. 4: 1) CUMULATIVE % DRUG RELEASE OF FORMULATIONS WITH GELUCIRE 43/01, CUMULATIVE PERCENTAGE DRUG RELEASE PROFILES OF FORMULATIONS WITH GELUCIRE 43/01, PMC K4M (F4) AND GELUCIRE 43/01, ETHYL CELLULOSE (F5 AND F6)

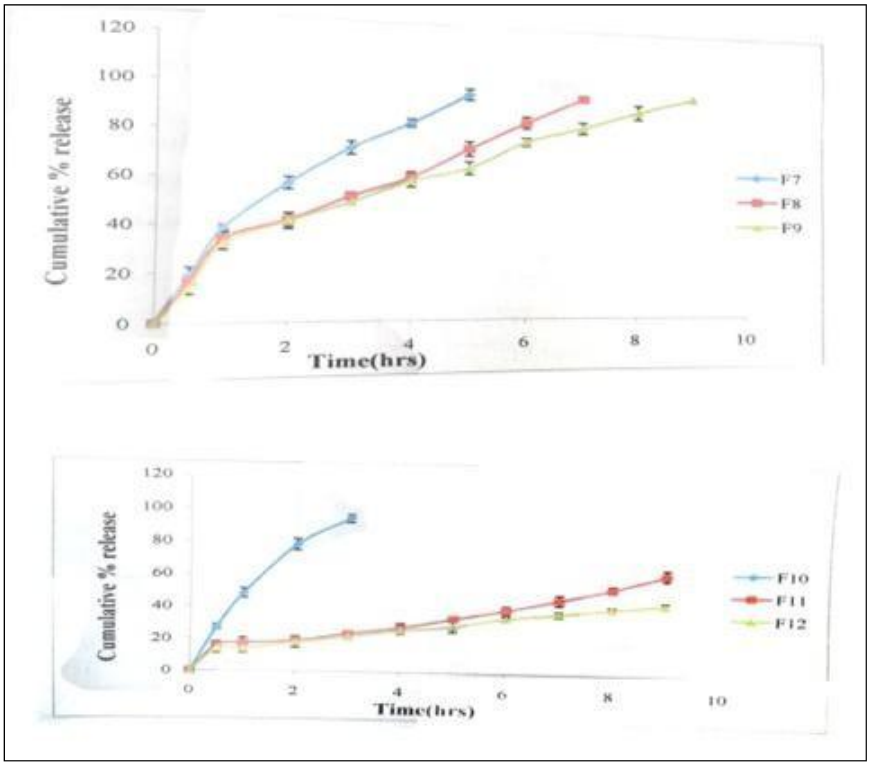


FIG. 5: 1) CUMULATIVE % DRUG RELEASE OF FORMULATIONS WITH CAMPRITOL 888 ATO, 2) CUMULATIVE PERCENTAGE DRUG RELEASE PROFILES OF FORMULATIONS WITH CAMPRITOL 888 ATO, HPMC K4M (F10) AND CAMPRITOL 888 ATO, ETHYL CELLULOSE (F11 AND F12)

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

RESULTS AND DISCUSSION:

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**.

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. Thesize 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: Researchers used FT-IR and DSC to determine that Amoxicillin trihydrate, lipids (Gelucire 43/01 and Campritol 888 ATO), and different types of polymers are compatible with one another. The regulated release and floating features of Formulations F3 and F9 were superior to those of other formulations.

The drug release followed a non-fickian process, as shown by the release exponent 'n' values, and there was no order to the drug release for F3 and F9. As a result, formulations containing Gelucire 43/01 outperformed those with Campritol 888 ATO in terms of release and floating. So, a multi-unit floating medication delivery system may benefit from using Gelucire 43/01.

REFERENCES:

1. 1. Mittal A: Cinnarizine Sustained-release Floating Granules: A Development and In-vitro Drug Release Profile; Pharma Tutor 2016; 4(8): 27-35.
2. 2. A Review on Self-Dispersing Formulations and Characterization by Rewar S, Bansal BK, Sharma AK, and Singh CJ. Research in the field of pharmaceutical and chemical sciences published in 2014, volume 1, issue 9, pages 52–62.
3. Hot melt granulation is a simple method for making monolithic osmotic release tablets (Panda, Tiwary, and Ashok, 2003). The article is published in 2012 in the journal Drug Development and Industrial Pharmacy and has a page number of 447–461.
4. A floating multiparticulate system of repaglinide was developed and evaluated in vitro by Rao MEB, Swain S, Patra CN, Sruti J, and Patra S. 2011; 36: 75-92 in FABAD Journal of Pharmaceutical Science.
5. 5. Shaha SH, Patelb JK, and Patel NV: Floating optimization utilizing factorial design for gatifloxacin-Gelucire 39/01. "Asian Journal of Pharmacy" 2010; 5(1): 35-43.

6. Particulate Science and Technology, 6. Thakare RS and Patil SB: Acyclovir Floating Granules Formulation, Development, and Optimization using the Melt Granulation Technique. 2015, volume 33, issues 3, pages 301-307.

7. 7. The Melt Granulation Technique for the Development and Evaluation of a Taste Masked Granular Formulation of Satranidazole by Pawar HA and Josi PR. The 2014 volume of the Journal of Pharmaceutics.

8. Floating matrix tablets containing diclofenac sodium were designed and evaluated in vitro using the melt granulation process (Chandra S., Gopi S., Alex BO, Elsayed ON, and Pavan OCS, 2008). Publication date: 2013; volume: 4, issue: 5. International Research Journal of Pharmacy.