Floating Granules of Ranitidine Hydrochloride-Gelucire 43/01: Formulation Optimization Using Factorial Design

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ABSTRACT

The purpose of this research was to develop and optimize a controlled-release multiunit floating system of a highly water soluble drug, ranitidine HCl, using Compritol, Gelucire 50/13, and Gelucire 43/01 as lipid carriers. Ranitidine HCl–lipid granules were prepared by the melt granulation technique and evaluated for in vitro floating and drug release. Ethyl cellulose, methylcellulose, and hydroxypropyl methylcellulose were evaluated as release rate modifiers. A 3^2 full factorial design was used for optimization by taking the amounts of Gelucire 43/01 (X_1) and ethyl cellulose (X_2) as independent variables, and the percentage drug released in 1(Q_1), 5(Q_5), and 10 (Q_{10}) hours as dependent variables. The results revealed that the moderate amount of Gelucire 43/01 and ethyl cellulose provides desired release of ranitidine hydrochloride from a floating system. Batch F4 was considered optimum since it contained less Gelucire and was more similar to the theoretically predicted dissolution profile (f_2 = 62.43). The temperature sensitivity studies for the prepared formulations at 40°C/75% relative humidity for 3 months showed no significant change in in vitro drug release pattern. These studies indicate that the hydrophobic lipid Gelucire 43/01 can be considered an effective carrier for design of a multiunit floating drug delivery system for highly water soluble drugs such as ranitidine HCl.

KEYWORDS: Multiunit lipid granules, Gelucire, ranitidine hydrochloride, floating.

INTRODUCTION

Rapid gastrointestinal transit can result in incomplete drug release from a device above the absorption zone, leading to diminished efficacy of the administered dose.[1] Therefore, different approaches have been proposed to retain the dosage form in the stomach. These include bioadhesive systems,[2] swelling and expanding systems,[3,4] and floating systems.[5,6] Large single-unit dosage forms undergo significant swelling after oral administration, and the swollen matrix inhibits gastric emptying even when the pyloric sphincter is in an uncontracted state. Park and Park reported on medicated polymeric sheets and swelling of balloon hydrogels.[7] But with swelling and expanding systems there is a risk of permanent retention. Bioadhesive systems may cause problems such as irritation of the mucous layer owing to high localized concentration of the drug.[8] Hydrodynamically balanced systems, designed using effervescent mixtures, have achieved commercial success but require a high drug:excipient ratio, have unpredictable bioavailability, and are unsuitable for drugs degrading in basic pH because of the alkaline microenvironment. Single-unit systems such as tablets or capsules may exhibit the all-or-none emptying phenomenon, which may be overcome by the design of multiunit systems.[9] Multiunit dosage forms such as pellets and granules may be more suitable because they claim to reduce the intersubject variability in absorption and lower the probability of dose dumping.[10] Many lipid-based sustained-release matrix systems are discussed in the literature.[11-14] Kumar et al reported on a floating glycerol monooleate single-unit lipid matrix containing a high drug:excipient ratio (1:30) to achieve sustained drug release.[15]

Gelucires are a family of vehicles derived from mixtures of mono-, di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires are available with a range of properties depending on their hydrophilic lipophilic balance (HLB 1-18) and melting point (33°C-65°C) range.[16,17] Gelucires containing only PEG esters (Gelucire 55/18) are generally used in the preparation of fast-release formulations, while Gelucires containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in the preparation of sustained-release formulations.[11,18] Sutananta et al reported on sustained-release single-unit matrices using Gelucire 43/01 where only 1.7% theophylline was released over 20 hours.[19] Recently, Shimpi et al[20] reported on a multiunit floating-dosage form of diltiazem HCl, considering the benefits of a multiunit floating dosage form over other systems.

Ranitidine HCl (RHCl), the model drug for this study, is a histamine H_2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. The recommended adult oral dosage of ranitidine is

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150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day.[21] A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours. An alternative dose of 300 mg leads to plasma fluctuations; thus, a sustained-release dosage form of RHCl is desirable.[22] The short biological half-life of the drug (~2.5-3 hours) also favors development of a sustained-release formulation. A traditional oral sustained-release formulation releases most of the drug at the colon; thus, the drug should have an absorption window either in the colon or throughout the gastrointestinal tract. Ranitidine is absorbed in only the initial part of the small intestine and has 50% absolute bioavailability.[23,24] Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon.[25] These properties of RHCl do not favor the traditional approach to sustained-release delivery. Hence, clinically acceptable sustained-release dosage forms of RHCl prepared with conventional technology may not be successful. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. It is also reported that oral treatment of gastric disorders with an H_2-receptor antagonist like ranitidine or famotidine used in combination with antacids promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the drugs' ability to reduce acid secretion.[26] This principle may be applied for improving systemic as well as local delivery of RHCl, which would efficiently reduce gastric acid secretion.

Thus, the major objective of the present study was to design floating sustained-release granules with a low drug:lipid ratio. To achieve a lower drug:excipient ratio and good floating ability, the hydrophobic grade of the lipid excipient Gelucire (Gelucire 43/01) was selected, and the formulation was optimized using a 3^2 full factorial design.

Materials and Methods

Materials

Gelucire 43/01 (waxy solid, melting point 43°C, HLB = 01) was a gift from Gattefosse (St Priest, Cedex, France). Ranitidine HCL was a gift from Astron Research Pvt Ltd (Ahmedabad, India). Ethyl cellulose (EC), methylcellulose (MC), and hydroxypropyl methylcellulose (HPMC) were gifts from Zydus Cadila HealthCare Ltd (Ahmedabad, India). Concentrated hydrochloric acid (HCL) was kindly supplied by Laser Chemicals (Ahmedabad, India). All other chemicals were of analytical grade.

Methods

Preparation of RHCl Floating Granules

Floating granules containing RHCl were prepared using the melt granulation technique. For factorial batches the drug was mixed with the required quantities of Gelucires (43/01) to produce the required drug:lipid ratio. The additives of different sustaining action—HPMC, EC, and MC—were added separately to the formulations. The lipid was melted at 50°C, and the drug or drug and additives mixture was added, mixed well, and cooled to room temperature. The mass was passed through a 22-mesh sieve to obtain uniform-sized granules.

Drug Content and Percentage Yield

Ten milligrams of floating granules were added to 10 mL of distilled water, heated to 60°C, and allowed to cool to room temperature. The lipid was solidified and the drug solution was filtered through Whatman filter paper (Whatman International Ltd., Maidstone, England). The sample was analyzed for drug content by UV spectrophotometry (Shimadzu UV/Vis double beam spectrophotometer, model 1601, Kyoto, Japan) at 313 nm after suitable dilutions. Drug stability in the dissolution medium was checked for a period of more than 12 hours. The percentage yield of each formulation was calculated.

In Vitro Evaluation of Floating Ability

A weight of granules equivalent to 336 mg of RHCl was placed in 900 mL of 0.1 N HCL in a vessel maintained at 37°C ± 0.5°C and stirred at 50 rpm in a US Pharmacopeia (USP) 24 type 2 dissolution test apparatus (Electrolab TDT-06T, Mumbai, India). The percentage of floating granules up to 12 hours was determined, and the floating times were measured by visual observation.

In Vitro Drug Release Studies

The release of drug from granules containing different drug:lipid proportions with and without the release rate modifier was investigated. Studies were performed in triplicate using a USP 24 type 2 dissolution test apparatus with an agitation speed of 50 rpm in 0.1 N HCL maintained at 37 ± 0.5°C. At appropriate time intervals, the samples were withdrawn and assayed spectrophotometrically at 313 nm after filtration through Whatman filter paper and suitable dilutions. The methodology for in vitro dissolution was kept the same for all the batches prepared.

Selection of Lipid Carrier

The preliminary screening was performed to test 3 materials as lipid carriers—Compritol, Gelucire 43/01, and Gelucire 50/13—using various drug-to-carrier ratios (1:0.5, 1:1, 1:1.5,

Table 1. Formulation and Evaluation of Batches in Full Factorial Design*

	Variable Levels in Coded Form†					
Batch Code	X_1	X_2	$Q_1 \pm SD$	$Q_5 \pm SD$	$Q_{10} \pm SD$	f_2 Value
F1	–1	1	42.59 ± 1.2	70.74 ± 2.1	94.39 ± 0.8	45.22
F2	–1	0	46.46 ± 0.9	82.53 ± 1.3	103.27 ± 2.6	35.52
F3	–1	–1	46.86 ± 0.8	92.09 ± 0.9	103.39 ± 2.3	28.41
F4	0	1	28.90 ± 1.1	68.18 ± 2.5	81.67 ± 1.2	62.43
F5	0	0	37.95 ± 1.7	73.77 ± 2.2	86.46 ± 0.9	48.49
F6	0	–1	41.86 ± 1.3	81.23 ± 1.8	96.06 ± 1.7	36.57
F7	1	1	26.22 ± 0.9	58.60 ± 1.2	71.41 ± 1.4	56.25
F8	1	0	29.46 ± 1.4	71.64 ± 2.1	85.51 ± 2.5	55.94
F9	1	–1	32.72 ± 2.3	76.97 ± 1.6	93.19 ± 1.9	42.08

	Actual Values†	
Coded Values	X_1	X_2
–1	504	84
0	672	168
1	840	252

*All batches contained 336 mg of ranitidine hydrochloride. SD is standard deviation of 3 determinations.
†X_1 indicates the amount of Gelucire 43/01 (mg); X_2, the amount of ethyl cellulose (mg).

and 1:2). The effect of polymers—EC, MC, and HPMC—on the release of drug from the granules was also checked at a drug:polymer ratio of 1:0.5. Granules prepared with different carriers and polymers were tested for floating behavior and in vitro drug release.

Optimization of Variables Using Factorial Design

A 3^2 randomized full factorial design was used in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The amounts of lipid (Gelucire 43/01, X_1) and release modifier (EC, X_2) were chosen as independent variables in the 3^2 full factorial design, while Q_1, Q_5, and Q_{10} (ie, drug release after 1, 5, and 10 hours, respectively) and similarity in dissolution profile of the prepared formulations to the theoretically predicted one (f_2 value) were selected as dependent variables. The formulation layout for the factorial design batches (F1-F9) is shown in Table 1, and their dissolution profiles are compared with the theoretically predicted ones in Figure 1.

Temperature Sensitivity Study of the Prepared Formulations

The final selection of the best formulation was done on the basis of the similarity factor (f_2 value). The batches with an f_2 value greater than 50 were considered to fit the required theoretical release pattern. Batches F4, F7, and F8 met this selection criterion. Among these batches, batch F4 was considered to be the best because it contained less Gelucire and showed a greater similarity in dissolution profile with theoretical predictions (f_2 = 62.43). To determine the change in in vitro release profile and floating behavior on storage, a temperature sensitivity study of the prepared formulations was performed at 40°C in a humidity jar with 75% relative humidity (RH). Samples were withdrawn after a 3-month interval and evaluated for change in in vitro drug release pattern and floating behavior.

Results and Discussion

Results of Preliminary Screening

The evaluation results for in vitro drug release showed that Compritol was unable to retard the drug release after 4 hours. Although the granules with Compritol were able to float for

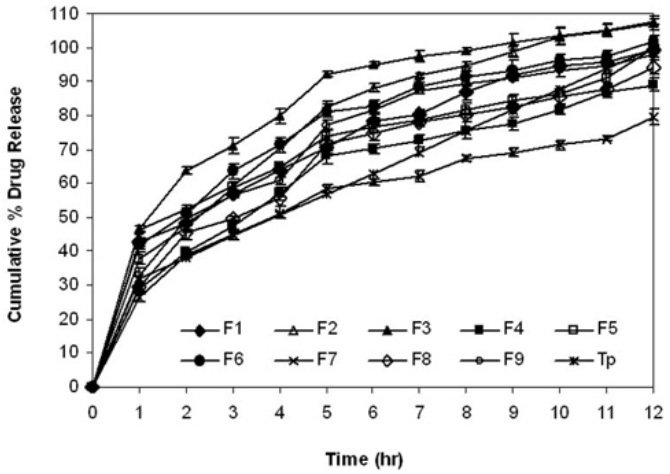

Figure 1. In vitro dissolution profile of prepared formulations.

Table 2. Summary of Results of Regression Analysis*

Coefficients for Q_1 Response (Q_1)	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	37.19	–7.91	–3.96	–0.56†	1.15†	–1.43†
RM	37.00	–7.91	–3.96	—	—	—
Coefficients for Q_5 Response (Q_5)	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	75.29	–6.36	–8.79	0.75†	1.04†	–1.35†
RM	75.08	–6.39	–8.79	—	—	—
Coefficients for Q_{10} Response (Q_{10})	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	89.22	–8.49	–7.53	–3.20†	3.79†	–1.73†
RM	90.59	–8.49	–7.53	—	—	—

*FM indicates full model; RM, reduced model.

†Response is insignificant at $P = 0.05$.

more than 12 hours, the drug was released completely within 4 hours. The granules prepared with Gelucire 50/13 were found to sink within 1 hour, with complete drug release in 2 hours. The granules prepared with Gelucire 43/01 in various ratios were found to float for more than 12 hours and to retard the drug release as a function of the amount of Gelucire 43/01; hence, Gelucire 43/01 was used for the further studies. To study the effect of various drug release modifiers from the granules, 3 batches were formulated using EC, MC, and low viscosity grade (K4M) HPMC. From the in vitro release study, EC was found to be the most effective in retarding the drug release. To evaluate the combined effect of Gelucire 43/01 and EC on the drug release from the granules, a full factorial design was used.

Full Factorial Design

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 \quad (1)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high values. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate nonlinearity. The dissolution profile for 9 batches showed a variation (ie, initial 1 hour release ranging from 26.22% to 46.86% and drug released after 12 hours ranging from 79.58% to 107.58%). The data indicate that the release profile of the drug is strongly dependent on the selected independent variables. The fitted equations (full and reduced) relating the responses Q_1, Q_5, and Q_{10} to the transformed factor are shown in Table 2. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and whether it is negative or positive. Table 3 shows the results of the analysis of variance that was performed to identify insignificant factors. The high values of correlation coefficients for Q_1, Q_5, and Q_{10} indicate a good fit. The equations may be used to obtain estimates of the response, as a small error of variance was noticed in the replicates. The significance test for regression coefficients was performed by applying the student F test. A coefficient is significant if the calculated F value is greater than the values of F.

Full and Reduced Model for Q_1

The significance levels of the coefficients b_{12}, b_{11}, and b_{22} were found to be $P = 0.7046$, 0.5864, and 0.5038, respectively, so they were omitted from the full model to generate a reduced model. The results of the statistical analysis are shown in Table 2. The coefficients b_0, b_1, and b_2 were found to be significant at $P < .05$; hence, they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_{12}, b_{11}, and b_{22} contribute significant information to the prediction of Q_1.[27] The results of the model testing are shown in Table 3. The critical value of F for $\alpha = 0.05$ is equal to 9.28 (df = 3, 3). Since the calculated value (F = 0.373) is less than the critical value (F = 9.28), it may be concluded that the interaction terms b_{12}, b_{11}, and b_{22} do not contribute significantly to the prediction of Q_1 and can be omitted from the full model to generate the reduced model. A response surface plot was also prepared, as shown in Figure 2.

Table 3. Calculations for Testing the Model in Portions*

Regression	DF	SS	MS	R^2	*P*	F_{cal} = 0.373 F_{table} = 9.28
For Q_1						
FM	5	478.03	95.60	0.9571	.0290	DF = (3, 3)
RM	2	470.05	235.02	0.9411	.0002	
Error						
FM	3	21.43	7.14			
RM	6	29.41	4.90			
For Q_5						
Regression	DF	SS	MS	R^2	*P*	F_{cal} = 0.345 F_{table} = 9.28
FM	5	714.66	142.93	0.9686	.0183	DF = (3, 3)
RM	2	706.68	353.34	0.9578	.000075	
Error						
FM	3	23.16	7.72			
RM	6	31.14	5.19			
For Q_{10}						
Regression	DF	SS	MS	R^2	*P*	F_{cal} = 4.238 F_{table} = 9.28
FM	5	848.17	169.63	0.9794	.0099	DF = (3, 3)
RM	2	772.53	386.26	0.8920	.0013	
Error						
FM	3	17.87	5.95			
RM	6	93.51	15.59			

*DF indicates degree of freedom; SS, sum of squares; MS, mean of squares; R^2, regression coefficient; FM, full model; RM, reduced model.

Full and Reduced Model for Q_5

The significance levels of the coefficients b_{12}, b_{11}, and b_{22} were found to be P = 0.6289, 0.6348, and 0.5427, respectively, so they were omitted from the full model to generate a reduced model. The results of the statistical analysis are shown in Table 2. The coefficients b_0, b_1, and b_2 were found to be significant at $P < .05$; hence, they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_{12}, b_{11}, and b_{22} contribute significant information to the prediction of Q_5.[27] The results of the model testing are shown in Table 3. The critical value of F for α = 0.05 is equal to 9.28 (df = 3, 3). Since the calculated value (F = 0.345) is less than the critical value (F = 9.28), it may be concluded that the interaction terms b_{12}, b_{11}, and b_{22} do not contribute significantly to the prediction of Q_5 and can be omitted from the full model to generate the reduced model. A response surface plot was also prepared, as shown in Figure 3.

Full and Reduced Model for Q_{10}

The significance levels of the coefficients b_{12}, b_{11}, and b_{22} were found to be P = 0.0791, 0.1152, and 0.3904,

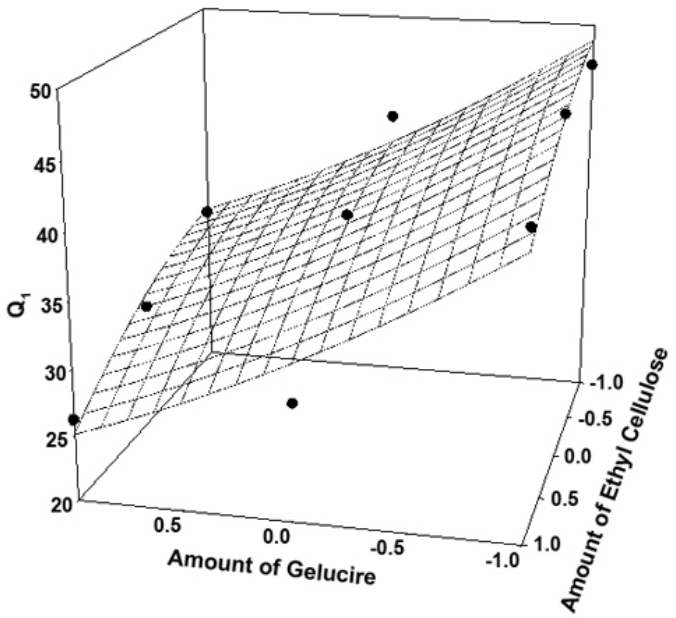

Figure 2. Response surface plot for Q_1.

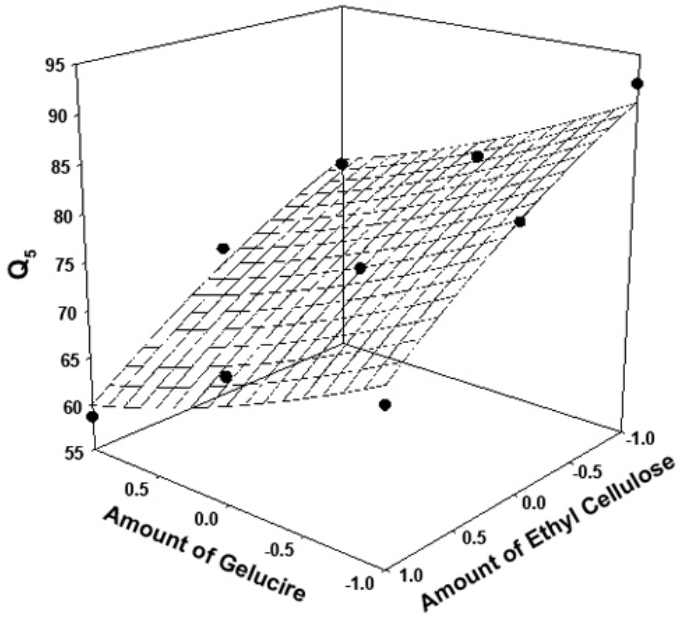

Figure 3. Response surface plot for Q_5.

respectively, so they were omitted from the full model to generate a reduced model. The results of the statistical analysis are shown in Table 2. The coefficients b_0, b_1, and b_2 were found to be significant at $P < .05$; hence, they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_{12}, b_{11}, and b_{22} contribute significant information to the prediction of Q_{10}.[27] The results of the model testing are shown in Table 3. The critical value of F for $\alpha = 0.05$ is equal to 9.28 (df = 3, 3). Since the calculated value (F = 4.238) is less than the critical value (F = 9.28), it may be concluded that the interaction terms b_{12}, b_{11}, and b_{22} do not contribute significantly to the prediction of Q_{10} and can be omitted from the full model to generate the reduced model. A response surface plot was also prepared, as shown in Figure 4.

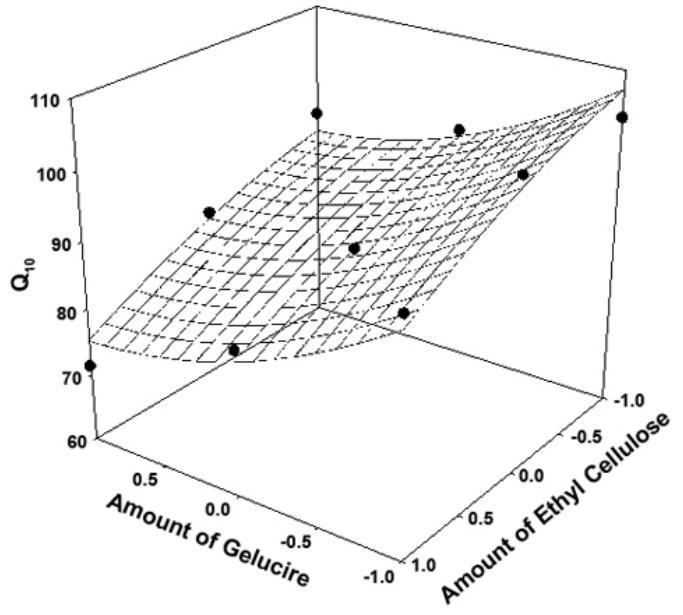

Figure 4. Response surface plot for Q_{10}.

Table 4. Results of Temperature Sensitivity Study of Batch F4*

Time (Hr)	Cumulative % Drug Release (Initial)	Cumulative % Drug Release (After storage at 40°C for 3 mo)
0	0.00	0.00
1	28.90	29.32
2	39.81	40.12
3	47.48	48.84
4	57.42	58.21
5	68.18	68.11
6	70.04	69.11
7	72.50	70.68
8	75.53	74.21
9	77.46	75.91
10	81.67	80.21
11	87.06	87.32

*Similarity factor (f_2): 91.41, dissimilarity factor (f_1): 1.57, $t_{cal} = 0.486$, $t_{tab} = 1.71$.

Results of Temperature Sensitivity Study

To determine the change in in vitro release profile on storage, a temperature sensitivity study of the prepared formulations was performed at 40°C in a humidity jar with 75% RH. Samples withdrawn after 3 months showed no change in in vitro drug release pattern and in vitro buoyancy. The value of the similarity factor for the best formulation (batch F4) was 91.41 (Table 4), indicating good similarity of dissolution profiles before and after temperature sensitivity studies. The calculated *t* value (0.486) was smaller than the tabulated *t* value (1.71), as shown in Table 4, indicating an insignificant difference in the dissolution profiles before and after temperature sensitivity studies.

CONCLUSION

From the present investigation it may be concluded that the hydrophobic lipid Gelucire 43/01 is an effective carrier for the design of a multiunit floating drug delivery system of highly water soluble drugs like RHCl.

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REFERENCES

1. Iannuccelli V, Coppi G, Bernabei MT, Cameroni R. Air compartment multiple-unit system for prolonged gastric residence, Part I: formulation study. *Int J Pharm.* 1998;174:47–54.

2. Santus G, Lazzarini G, Bottoni G, et al. An *in vitro-in vivo* investigation of oral bioadhesive controlled release furosemide formulations. *Eur J Pharm Biopharm.* 1997;44:39–52.

3. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: an overview. *Drug Dev Ind Pharm.* 1996;22:531–539.

4. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. *Pharm Res.* 1997;14:815–819.

5. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. *J Pharm Sci.* 1994;83:239–245.

6. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. *J Control Release.* 1998;55:3–12.

7. Park K, Park H. Enzyme digestible balloon hydrogel for long term oral drug delivery: synthesis and characterization. *Int Symp Rel Bioact Mater.* 1987;14:41–42.

8. Ch'Ng HS, Park H, Kelly P, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery, II: synthesis and evaluation of some swelling water-insoluble bioadhesive polymers. *J Pharm Sci.* 1985;74:399–405.

9. Kaniwa N, Aoyagi N, Ogata H, Ejima A. Gastric emptying of enteric coated drug preparations, II: effect of size and density of enteric coated drug preparations and food on gastric emptying rates in humans. *J Pharmacobiodyn.* 1988;11:571–575.

10. Efentakis M, Koutlis A, Vlachou M. Development and evaluation of oral multiple-unit and single-unit hydrophilic controlled-release systems. *AAPS PharmSciTech.* 2000;1:E34.

11. Dennis AB, Farr SJ, Kellaway IW, Taylor G, Davidson R. In vivo evaluation of rapid release and sustained release Gelucire capsule formulations. *Int J Pharm.* 1990;65:85–100.

12. Remunan C, Bretal M, Nunez A, Bila Jato JL. Accelerated stability of sustained release tablet prepared with Gelucire. *Int J Pharm.* 1992;80:151–159.

13. Saraiya D, Bolton D. The use of Precirol to prepare sustained release tablets of theophylline and quinidine gluconate. *Drug Dev Ind Pharm.* 1990;16:1963–1969.

14. Li S, Lin S, Chien YW, Daggy BP, Mirchandani HL. Statistical optimization of gastric floating system for oral controlled delivery of calcium. *AAPS PharmSciTech.* 2001;2:E1.

15. Kumar MK, Shah MH, Ketkar A, Mahadik KR, Paradkar A. Effect of drug solubility and different excipients on floating behavior and release from glyceryl monooleate matrices. *Int J Pharm.* 2004;272:151–160.

16. Aïnaoui A, Vergnaud JM. Modelling the plasma drug level with oral controlled release forms with lipidic Gelucire. *Int J Pharm.* 1998;169:155–162.

17. Sheu MT, Hsia AHO. Polyglycolized saturated glycerides as carrier and enhancer for drug penetration. *Chin Pharm J.* 2001;53: 107–111.

18. Barker SA, Yap SP, Yuen KH, McCoy CP, Murphy JR, Craig DQM. An investigation into the structure and bioavailability of α-tocopherol dispersion in Gelucire 44/14. *J Control Release.* 2003;91:477–488.

19. Sutananta W, Craig DQM, Newton JM. An evaluation of the mechanisms of drug release from glyceride bases. *J Pharm Pharmacol.* 1995;47:182–187.

20. Shimpi S, Chauhan B, Mahadik KR, Paradkar A. Preparation and evaluation of diltiazem hydrochloride-Gelucire 43/01 floating granules prepared by melt granulation. *AAPS PharmSciTech.* 2004;5:E43.

21. Flynn M. Histamine H2 antagonists. In: Hagemann RC, Threlkeld DS, eds. *Drug Facts and Comparisons.* 50th ed. St Louis, MO: Wolters Kluwer Co; 1996:1862–1876.

22. Somade S, Singh K. Comparative evaluation of wet granulation and direct compression methods for preparation of controlled release ranitidine HCL tablets. *Indian J Pharm Sci.* 2002;64:285.

23. Lauritsen K. Clinical pharmacokinetics of drugs used in the treatment of gastrointestinal diseases. *Clin Pharmacokinet.* 1990;19:11–31, 94–125.

24. Grant S. Ranitidine: an updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in peptic ulcer disease and other allied diseases. *Drugs.* 1989;37:801–870.

25. Basit A, Lacey L. Colonic metabolism of ranitidine: implications for its delivery and absorption. *Int J Pharm.* 2001;227:157–165.

26. Coffin M, Parr A, inventors. Glaxo Inc. Ranitidine solid dosage form. US patent 5 407 687. April 18, 1995.

27. Mendenhall W, Sincich T, eds. Multiple regression. In: *A Second Course in Business Statistics, Regression Analysis.* 3rd ed. San Francisco, CA: Dellen Publishing Co; 1989:141–226.