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Full Length Research Paper

An innovative approach to prolong gastric retention:- "Floating microspheres of cimetidine hydrochloride"

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The purpose of this research work was to developed and optimize a controlled-release multiunit floating system of a freely water soluble drugs such as (CHCL). Cimetidine is a histamine H_2-receptor antagonist that inhibits the production of acid in the stomach. It is largely used in the treatment of heartburn and peptic ulcers Oral delivery of the water soluble drug is so far the most preferable and ease route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations, but immediate release to site-specific delivery, oral dosage form has really progressed as compaired to novel dosage forms. Various attempts have been made to develop gastro-retentive delivery systems. For example floating, swelling, mucoadhesive, and high-density system. These systems have more flexibility in dosage design than conventional dosage form Cimetidine-HCL lipid microspheres 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.

Keywords: Floating Microspheres, H2 Receptor, Tagamet HB or Tagamet HB200

INTRODUCTION

Designing of oral control drug delivery systems (ODDS) should be primarily required to achieve more predictable and increased bioavailability Garima Chawla et al. (2003).so different systems have been proposed to retain the dosage form in the stomach. These include bioadhesive / mucoadhesiv systems Santus G et al. (1997), swelling and expanding systems, Deshpande AA et al. (1996), Deshpande AA et al. (1997), Menon A (1994) and floating systems Whitehead l et al. (1998).

Three decades, various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time:

1. Bioadhesive/Mucoadhesive Systems: (Ikeda k et al. 1992; Nagai T et al. 1998; Illum l et al. 1998; Schaefer MJ; Hannah B 2004; Garg S and Sharma S 2003; Chawla G et al 2001; Chickering DE et al. 1995; Seng CH 1995; Yyas SP and Roop Khar K 2002; Garg S and Sharma S 2003; Jain N K 2004; Efentakis M et al. 2000)
2. Swelling Systems
3. Floating Systems

Along with floating microspheres, other dosage form like Multiunit dosage forms such as pellets and microspheres may be more suitable because they claim to reduce the intersubject variability in absorption and lower the probability of dose dumping Kumar MK et al (2004). Mr. 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 Kumar MK et al (2004), Anjou A and Vergnaud JM (1998).

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Gelucires are a folks of vehicles resultant from mixtures of mono-, di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires are accessible with a range of properties depending on their hydrophilic lipophilic balance (HLB 1-18) and melting point (M.P.33℃-65℃) range Sheu MT and Hsia AHO (2001), Barker SA et al (2003). Gelucires contain only PEG esters (Gelucire 55/18) are normally used in the groundwork of fast-release formulations, while Gelucires contain only glycosides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in the preparation of sustained-release formulations Sutananta W et al (1995), Shimpi S et al. (2004). A multiunit floating-dosage form of diltiazem HCl, bearing in mind the benefits of a multiunit floating dosage form over other systems.[26,27] Sustained-release single-unit matrices using Gelucire 43/01 where only 1.7% theophylline was released over 20 hours Sheu MT and Hsia AHO (2001), Barker SA et al (2003), Sutananta W et al (1995), Shimpi S et al. (2004), Flynn M (1996), Somade S and Singh K (2002), Silverman and Richard A (2004).

Cimetidine HCL take as a model drug for study of various parameters, Cimetidine is the prototypical histamine H_2-receptor antagonist from which the later members of the class are developed Flynn M (1996). It is broadly prescribed in active duodenal ulcers, Zollinger-Ellison syndrome, gastric ulcers gastro esophageal reflux disease, and erosive esophagi are. The recommended adult oral dosage of cimetidine is 130 mg twice daily or 250 mg once daily Whitney Jake (2006).

Chemical data	
Formula	$C_{10}H_{16}N_6S$
Mol. mass	252.34 g/mol

Cimetidine inhibits the CYP-450 enzyme, and metabolism mainly occurs in the liver by cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP3A4. Due to the inhibition of the CYP-450 enzyme, THC, the psychoactive substance in Cannabis, would not be able to be metabolized until the inhibition of the CYP-450 enzyme is lifted, which may take hours, thus increasing the duration of its effect. Cimetidine has been found to reduce the debilitating pain and symptoms of herpes zoster, presumably by blocking the H_2-receptors of T-lymphocyte suppressor cells Hirtz J (1985).

Therefore, the foremost purpose of the present study was to design floating sustained-release microspheres with a low drug: lipid ratio. To attain a lower drug: excipient ratio and good floating capability.

MATERIALS

Gelucire 43/01 (waxy solid, melting point about 42℃, HLB = 01) was a gift from Torrent research centre (Ahamdabad). Cimetidine HCL was a gift from Aristo Pvt Ltd (Bhopal) Ethyl cellulose (EC), methylcellulose (MC), hydroxypropyl methylcellulose (HPMC) concentrated hydrochloric acid (HCL) was gifted from Aristo Pvt Ltd (Bhopal). All other chemicals were of analytical grade.

METHODS

Preparation of Cimetidine Hydrochloride (CHCL) Floating microspheres

Floating microspheres of CHCL were prepared by means of the thaw granulation technique or melt granulation technique. For selected batches the Cimetidine was mixed with the necessary quantities of Gelucires (43/01) to construct the required drug: lipid proportion. The additives of different sustaining action—EC, HPMC, and MC—were added individually to the formulations. The lipid was melt at about 50℃, and the drug and additives mixture was added. Then mixed well, and cooled at room temperature (RT). The mass was passed through a 22-mesh sieve to obtain uniform-sized microspheres.

Drug Content and Percentage Yield

10 milligrams of floating microspheres were added to 10 mL of distilled water, then heated it to around 60℃, and then allowed to cool at room temperature. The lipid was solidified and the drug solution was filtered through Whatman filter paper. The sample was analyzed for drug content by UV spectrophotometry (Shimadzu UV/Vis double beam spectrophotometer) at 313 nm after suitable dilutions. Drug stability in the dissolution medium was checked for a period of more than 10 hours. The percentage yield of each formulation was calculated.

In Vitro Evaluation of Floating Ability

A weight of microspheres equivalent to 330 mg of CHCl was placed in 900 mL of 0.1 N HCL in a vessel maintained at 37℃ ± 0.5℃ and stirred at 50 rpm in a USP type 2 dissolution test apparatus .The percentage of floating microspheres up to 10 hours was determined, and the floating times were measured by visual observation.

In Vitro Drug Release Studies

Drug release from the microspheres containing different drug: lipid proportions with and without the release rate modifier was investigated. Studies were performed in triplicate using a USP type 2 dissolution test apparatus with an agitation speed of 50 rpm in 0.1 N HCL maintained at 37 ± 0.5℃. At appropriate time intervals,

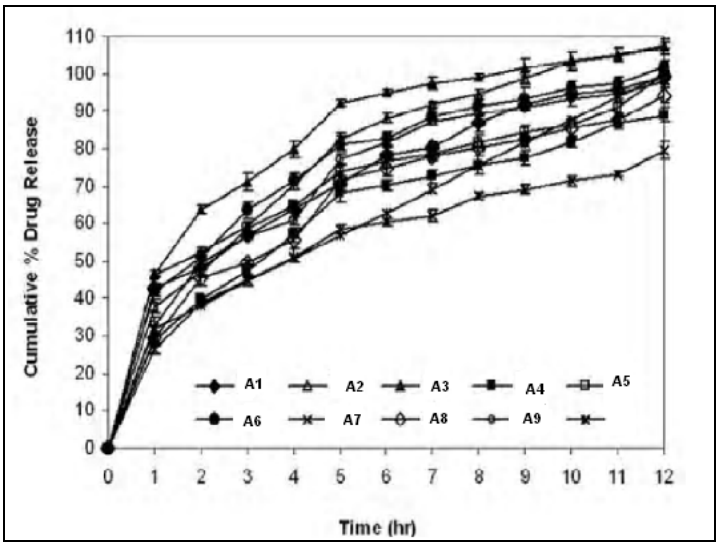

Figure 1 In-vitro drug release profile of prepared microspheres:

the samples were introverted 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. Figure 1

Assortment of Lipid Carrier

The first round screening was performed to test 3 materials as lipid carriers—Compritol, Gelucire 43/01, and Gelucire 50/13—using various drug-to-carrier ratios (1:0.4, 1:8, 1:1.0, and 1:5). The effect of polymers—MC, EC, and HPMC—on the release of drug from the microspheres was also tartan at a drug: polymer ratio of 1:1. Microspheres prepared with different carriers and polymers were tested for floating behavior and in-vitro drug release of drug.

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 combination. The amounts of lipid (Gelucire 43/01) and release modifier (EC) were chosen as independent variables in the 3^2 factorial design, while R_1,R_4 R_8 and R_{10} (i.e., drug release after 1, 4, and 8 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 (B1-B9) is shown in Table 1, and their dissolution profiles are compared with the theoretically predicted ones in

High temperature Sensitivity Study of the Prepared Microspheres

The finishing 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. To determine the change in vitro release profile and floating behavior on storage, a temperature sensitivity study of the prepared formulations was performed at 41°C in a humidity jar with 74% relative humidity (RH). Samples were withdrawn after a 20-days interval and evaluated for change in vitro drug release pattern and floating behavior.

RESULTS AND DISCUSSION

The assessment consequences for in vitro drug release showed that Compritol was unable to retard the drug release after 4 hours. Although the microspheres with Compritol were able to float for more than 10 hours, the drug was released completely within 3.45 hours. The microspheres prepared with Gelucire 50/13 were found to sink within 1 hour, with complete drug release in 2 hours. The microspheres prepared with Gelucire 43/01 in various ratios were found to float for more than 11 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 microspheres, 2 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

Table 1

Batch Code	Variable Levels		R_1 ± SD	R_4 ± SD	R_8 ± SD	f_2 Value
	Amount of Gelucire 43/01	Amount of EC(mg)				
B1	504	252	41.99 ± 1.2	71.74 ± 2.1	93.39 ± 0.8	45.22
B2	504	168	45.96 ± 0.9	81.53 ± 1.3	101.27 ± 2.6	35.52
B3	504	84	47.16 ± 0.8	93.09 ± 0.9	102.39 ± 2.3	28.41
B4	672	252	27.90 ± 1.1	69.18 ± 2.5	91.67 ± 1.2	62.43
B5	672	168	38.95 ± 1.7	74.77 ± 2.2	89.46 ± 0.9	48.49
B6	672	84	40.89 ± 1.3	79.23 ± 1.8	98.06 ± 1.7	36.57
B7	840	252	27.20± 0.9	60.60 ± 1.2	69.41 ± 1.4	56.25
B8	840	168	28.96 ± 1.4	70.64 ± 2.1	86.51 ± 2.5	55.94
B9	840	84	32.72 ± 2.3	75.97 ± 1.6	94.19 ± 1.9	42.08

Table 2

Time in (Hr)	Cumulative % Drug Release (Initial)	collective % Drug Release (After storage at 41°C for 20 DAYS)
0	0.00	0.00
1	27.89	28.22
2	36.80	47.72
3	44.49	45.14
4	53.41	54.11
5	63.38	65.01
6	69.28	70.33
7	70.69	71.18
8	72.39	73.17
9	75.62	74.99
10	78.74	79.71
11	82.56	83.82

on the drug release from the microspheres, a full factorial design was used.

Results of Temperature Sensitivity Study

To determine change in in-vitro release profile on storage, a temperature sensitivity study of the prepared formulations was performed at 41°C in a humidity jar with 74% RH. Samples withdrawn after 20 days that showed no change in in-vitro drug release pattern and in vitro optimism. The value of the similarity factor for the best formulation was 89.62 Table 2, 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 2, indicating an insignificant difference in the dissolution profiles before and after temperature sensitivity studies.

CONCLUSION

The current investigation it may be finished 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 CHCl.

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