Research Article

Int J. Pharm. Drug. Anal, Vol: 11, Issue: 3, 2023; 86-91

International Journal of Pharmaceutics and Drug Analysis

Content Available at www.ijpda.com ISSN: 2348:8948

FORMULATION AND IN-VITRO EVALUATION OF FLOATING PULSATILE DRUG DELIVERY OF CHRONOTHERAPEUTIC RELEASE OF H2 RECEPTOR ANTAGONIST OF FAMOTIDINE

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Received: 06 July 2023 Revised: 16 Aug 2023 Accepted: 25 Sept 2023

Abstract

In the present study famotidine floating pulsatile drug delivery system was developed. Various type and different concentrations of superdisintegrants and polymer affect the drug release. FTIR studies concluded that there is no interaction between drug and excipients. Based on disintegration time and dissolution time the formulation (F2) which contains 8% sodium starch glycollate was optimised. The optimised formulation F2 was further coated with different concentrations of HPMC K4M,HPMC K 15M and HPMC K 100M..Based on the concentration of the coating layer and solubility of the coating layer and the dissolution data the formulation (F6) which was coated with 150mg of HPMC K 15M was optimised.

Keywords: Famotidine, Flaoting, Pulsatile, HPMC.

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DOI: https://doi.org/10.47957/ijpda.v11i3.556

Produced and Published by

South Asian Academic Publications

Introduction

Chronotherapeutics is the delivery of medications in the right concentration to the right targeted tissues at the right time to meet biological rhythm-determined needs, e.g., rhythms in the mechanisms of disease, symptom intensity, and/ or patient tolerance, to optimize desired and minimize and avert adverse effects [1].

Introduction to Chronopharmacokinetics:

Chronopharmacokinetics describes biologic time-related changes in the pharmacokinetics of an agent [2]. The time of administration of a drug or toxic agent may influence the response of the organism [3]. Chronopharmacology examines the influence of the moment of drug administration (hour, month, and year) on the drug and body response according to the temporal structure of the organism receiving it [4]. Thus, the quantitative response (duration or intensity of the action) of an organism, as well as the qualitative response (i.e. inhibition or induction, increase or decrease of its effect), varies with time of administration [5].

Chronotherapy-Pulsatile drug delivery systems (PDDS)

The knowledge of 24 hr rhythm in the risk of disease plus evidence of 24 hr rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for pharmacotherapy (chronotherapy) [6]. One approach to increasing the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and/or best tolerated [7]. The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity [8].

Methodologies

Various techniques are available for the pulsatile delivery, broadly classified as single-unit and multiple-unit systems. Overall, they work on same basic principles of erosion or dissolution; swelling and rupturing; and system based on change in membrane permeability [9].

General methodologies for the pulsatile drug delivery system can be broadly classified into three classes;

1. Time controlled
2. Stimuli induced
3. Externally regulated
4. Time controlled pulsatile release system

Floating Pulsatile Drug Delivery Systems

Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Various diseases like asthma, hypertension, and arthritis show circadian

variation that demand time-scheduled drug release for effective drug action [10].

Conventional pulsatile release dosage forms following oral administration are meant to release drug after a lag period of 56 h usually in the small or large intestine. However, the viscous contents of lower part of GI tract cause hindrance to the drug diffusion and also enzymatic degradation of some drugs makes it an unfavourable site for drug release [11]. 67 Further, highly variable nature of gastric emptying process may result in in vivo variability and bioavailability problems [12]. In contrary, gastro-retentive dosage forms reside in stomach only and are not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach [13]. These considerations led to the development of pulsatile release dosage forms possessing gastric retention capabilities.

Gastro Retentive Drug Delivery Systems

Majority of the drugs are well absorbed from all the regions of the G.I tract while some are absorbed only from specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, as well as to the degradation of the drug by the microorganisms present in the colon [14]. Therefore, in instances where the drug is not absorbed uniformly over the G.I tract, the rate of drug absorption may not be constant in spite of the drug delivery system delivering the drugs at a constant rate into the G.I fluids. More particularly, in instances where a drug has a clear cut absorption window i.e. the drug is absorbed only from specific regions of the stomach or upper parts of the small intestine, it may not be completely absorbed when administered in the form of a typical oral controlled drug delivery system [15]. It is due to the relatively brief gastric emptying in humans, which normally averages 2-3 hrs through the major absorption zone [16]. It may cause incomplete drug release from the dosage form at absorption sites leading to diminished efficacy ofthe administered *dose [17].* It is apparent that for a drug having such an absorption window, an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for *a* long period of time [18]. For this drug, increased or more predictable availability would result if controlled release systems could be retained in the stomach for extended periods of time [19].

Materials and methods

Name of the material	Source
Famotidine	SURA LABS
Microcrystalline cellulose	Signet Chemical Corporation, Mumbai, India.
Sodium starch glycollate.	Merck Specialities Pvt Ltd, Mumbai, India
Croscarmellose sodium.	Merck Specialities Pvt Ltd, Mumbai, India
Crospovidone	Merck Specialities Pvt Ltd, Mumbai, India
PVP K-30	Merck Specialities Pvt Ltd, Mumbai, India
Magnesium stearate	Merck Specialities Pvt Ltd, Mumbai, India
Talc	Merck Specialities Pvt Ltd, Mumbai, India
Eudragit L100	Merck Specialities Pvt Ltd, Mumbai, India
Eudragit S 100	Merck Specialities Pvt Ltd, Mumbai, India
Triethyl citrate	Merck Specialities Pvt Ltd, Mumbai, India
Acetone	Merck Specialities Pvt Ltd, Mumbai, India
Isopropylalcohol	Merck Specialities Pvt Ltd, Mumbai, India

Formulation of compressed tablets of Famotidine

Optimization of gas generating agent

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on that the concentration of sodium bicarbonate was finalized and preceded for further formulations.

S.No.	Ingredients	EF1	EF2	EF3
1	*Famotidine*	40	40	40
2	HPMC K 100M	40	40	40
3	NaHCO3	40	40	40
4	Mg.Stearate	100	100	100
5	Talc	100	100	100
6	MCC pH 102	100	100	100

***P*reparation of core tablets**

Core tablets of Famotidine were formulated by incorporating super disintegrants like sodium starch glycollate, and crospovidione, MCC and lactose (diluent), magnesium stearate and talc etc.

All the ingredients were accurately weighed as per formula and were dispensed in clean polythene cover, mixed well and sieved through 60mesh and subjected to compression. Direct compression of tablets was done in rotary compression tablet machine (Rimek mini press I) using 6 mm concave punch.

Table no. 6.3. Composition of various tablet formulations

Ingredients	F1	F2	F3	F4	F5	F 6
Famotidine*(mg)*	40	40	40	40	40	*4 0*
SSG*(mg)*	6	8	10	-	-	-
CP*(mg)*	-	-	-	6	8	*1 0*
Mg *St(mg)*	2	2	2	2	2	2
Talc(mg*)*	2	2	2	2	2	2
MCC*(mg)*	*3*	3	3	3	3	3
Lactose *(mg)*	Qs	Qs	Qs	Qs	Qs	Q s
Totalwt*(mg)*	100	100	100	100	100	1 0 0

Compression Coating of tablets

Components of the coat were mixed for 10 minutes. Die filling, core centralization and machine operation were undertaken using by a standardized manual process20. Half of the powder mass for one tablet coat was weighed into a die. A lower coating layer was consolidated and the core centered on an even bed. The remaining powder was then added to the die and compressed in to tablets using single punch tablet machine in concave punch (Diameter 9mm).

Coatinging redients	F P 1	*F P* 2	F P 3	F P 4	F P 5	F P 6	F P 7	F P 8	F P 9
HPMC *K 4M*	5 0	1 0 0	1 5 0	-	-	-	-	-	-
HPMC *K 15 M*	-	-	-	5 0	1 0 0	1 5 0	-	-	-
HPMC *K 100M*	-	-	-	-	-	-	5 0	1 0 0	1 5 0
Sodiumbic arbonate	5 0	5 0	5 0	5 0	5 0	5 0	5 0	5 0	5 0
Total weight	2 5 0	2 5 0	2 5 0	2 5 0	2 5 0	2 5 0	2 5 0	2 5 0	2 5 0

All ingredients weight in mg

Various in-vitro tests performed are

Weight variation test

Uniformity of thickness

Hardness

In-vitro buoyancy test

Disintegration

Dissolution

Drug content estimation

Results and discussion

In-vitro drug release studies were carried out for 8hrs and found to be good sustaining efficacy. The dissolution study was carried out in 0.1N HCL. In that first 3 formulations prepared with HPMC K 4M when the concentration of polymer increases the retardation of drug release not released up to 8 hours. Whereas the floating pulsatile tablets prepared with HPMC K 15 M the drug release up to 8 hours (FP6 formulation 96.38%).

Where in pulsatile coated tablets with HPMC K 100M the retardation of drug release is more than 8 hours so it z not considered for good formulation. Using various polymers like HPMC K4M, HPMC K15M and HPMC K100M, the floating pulsatile famotidine tablets were prepared along with other additives. Direct compression method was used for the preparation of tablets. A total number of 20 formulations were prepared and evaluated.

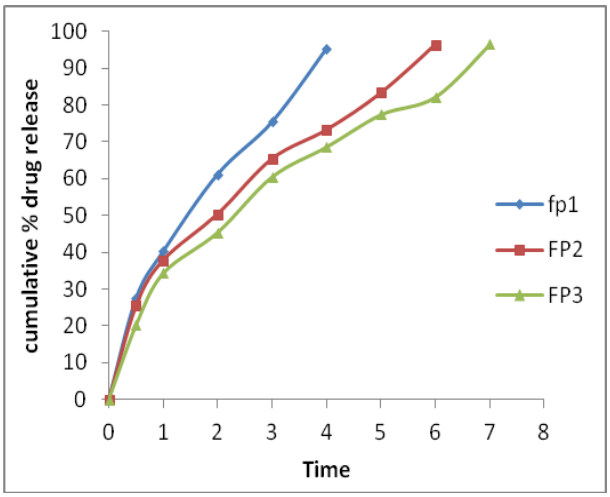
Tableting characteristics of floating pulsatile famotidine tablets.

Formulation	Thickness *(mm)*	Hardness *(Kg/cm2)*	Weightvariation *(mg)*	Friability *(%) n=10*	Drug content *(%) n=5*
F1	3.88± 0.116	4.57± 0.193	301±0.588	0.52	96.68
F2	3.85± 0.102	4.28± 0.37	311±0.639	0.56	96.74
F3	4.31± 0.13	4.34±. 175	298.4±0. 573	0.53	97.21
F4	4.28± 1.24	4.52± 0.429	290.54±0 .71	0.54	95.37
F5	3.86± 0.23	4.53± 0.42	296.3±0. 12	0.45	97.56
F6	3.75± 0.44	4.74± 0.54	290.43±0 .43	0.65	99.45
F7	3.81± 0.53	4.41± 0.43	310.34±0 .54	0.75	100.2 3
F8	4.12± 1.12	4.56± 0.54	290.4±0. 52	0.60	95.48
F9	4.25± 0.34	4.1±0. 43	302±1.04	0.64	97.45

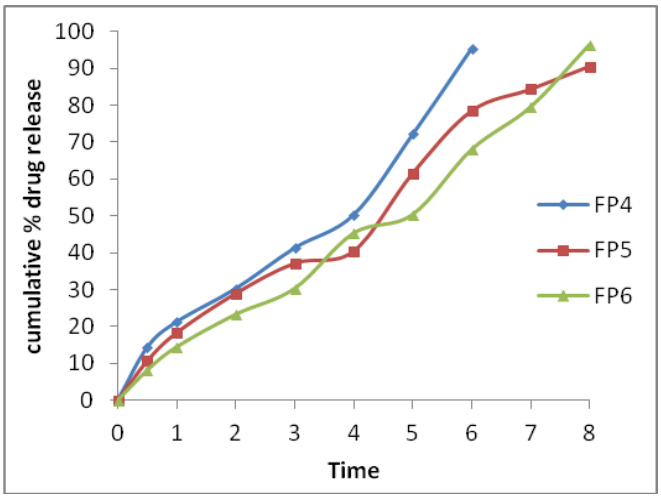
Evaluation of thickness, hardness and wt variation of coated tablets

Time	FP *1*	FP *2*	FP *3*	FP *4*	FP *5*	FP *6*	FP *7*	FP *8*	FP *9*
0.5	27.45	25.37	20.14	14.38	10.63	8.14	10.53	8.43	7.35
1	40.25	37.84	34.27	21.27	18.28	14.45	20.16	7.35	14.23
2	61.23	50.37	45.37	30.27	28.91	23.27	35.27	17.34	20.36
3	75.46	65.38	60.47	41.28	37.09	30.28	40.27	14.23	33.26
4	95.43	73.27	68.58	50.26	40.37	45.27	55.28	23.02	40.38
5		83.29	77.38	72.10	61.45	50.29	78.25	20.36	49.23
6		96.41	82.17	95.37	78.38	67.92	82.36	36.10	54.10
7			96.49		84.27	79.46	90.36	33.26	60.38
8					90.46	96.38		45.38	73.27

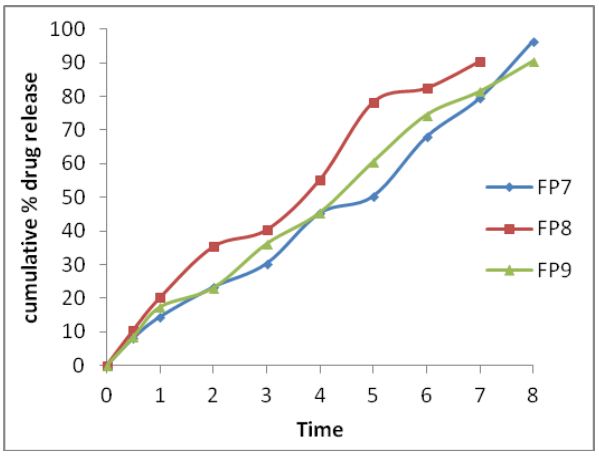
Cumulative percentage drug release of coated tablets with 0.1N HCl and phosphate buffer 6.8ph



*C*umulative Percentage drug release of floating pulsatile coated tablets with HPMC K4M polymer (fp1-fp3)



Cumulative Percentage drug release of floating pulsatile coated tablets with HPMC *K15M* polymer *(*fp4-fp6*)*



Cumulative Percentage drug release of floating pulsatile coated tablets with HPMC K100M polymer (fp7-fp9)

Famotidine blend was subjected to various pre-formulation parameters. The apparent bulk density and tapped bulk density values ranged from 0.69 to 0.71 and 0.79 to 0.81 respectively. According to Tables 7.3, the results of angle of repose and compressibility index (%) ranged from 25.28 to 29.05 and 12.12 to 14.55 respectively. The results of angle of repose (<35) and compressibility index (<23) indicates fair to passable flow properties of the powder mixture. These results show that the powder mixture has good flow properties. The formulation blend was directly compressed to tablets and in-vitro drug release studies were performed.

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet. Total weight of tablet including core is 100 mg.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

The in-vitro drug release study for core tablets was carried out in 0.1N HCL as dissolution medium for about 60min.The drug release from the formulations increased as the concentration of super disintegrant increased. Based on the results obtained F2 formulation which was formulated by using 8% Sodium starch glycollate was found to be 96.79% within 20min and selected for further press coating method.

In-vitro drug release studies were carried out for 8hrs and found to be good sustaining efficacy. The dissolution study was carried out in 0.1N HCL. In that first 3 formulations prepared with HPMC K 4M when the concentration of polymer increases the retardation of drug release not released up to 8 hours. Whereas the floating pulsatile tablets prepared with HPMC K 15 M the drug release up to 8 hours (FP6 formulation 96.38%).

Where in pulsatile coated tablets with HPMC K 100M the retardation of drug release is more than 8 hours so it z not considered for good formulation.

Summary and conclusion

The present work aimed to developing coated famotidine formulations floating pulsatile using HPMC K4M, HPMC K15M and HPMc K100M. All the formulations were evaluated for physicochemical properties and in-vitro drug release studies.

The drug and excitement comparability were performed, and the excipient selected for formulation are found to be stable and there is no interaction between the drug and excipient. The active pharmaceutical ingredient, it was characterized for physicochemical characteristics like, bulk density, tapped density, compressibility index etc. Famotidine shows better solubility in 0.1N Hcl. The drug substances exhibits good flow properties. All the formulations were analysed for the preformulation parameters such as bulk density, true density, compressibility index, hausners ratio, angle of repose and the results were found to be within the limits. All the formulations were compressed into tablets and were analysed for the parameters such as average weight, percentage of drug content, friability, hardness, thickness and the results were found to be within the limits. An in-vitro dissolution study for all formulations was carried out in 0.1NHcl for 8hours and the percentage drug release was calculated.

Various type and different concentrations of super disintegrants and polymer affect the drug release. FTIR studies concluded that there is no interaction between drug and excipients. Based on dissolution time the formulation (F2) which contains 8% sodium starch glycollate was optimised. The optimised formulation F2 was further coated with different concentrations of polymers like HPMC K4M, HPMC K15M, HPMC K100M. Based on dissolution results HPMC K15M showed good release (96.38% at 8hrs) so F6 formulation is optimised formulation and drug release kinetics applied on best formulation and it follows zero order release kinetics.

Funding

No Funding

Acknowledgement

Conflict of Interest

There is no conflict in between the authors.

Informed Consent &Ethical Statement

Not Applicable

Author Contribution

Asiya Shaik, first author has executed & designed data, has done the complete work. D.Nirmala second author. Has helped in the calculation part.

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