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Research paper

FORMULATION DEVELOPMENT AND IN-VITRO EVALUATION OF GELUCIRE BEADS OF RAMIPRIL

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The purpose of this research was to develop floating Gelucire beads of Ramipril. Ramipril is slightly soluble in water. It is having 2-4 hour half life. Protein binding is 73% and 56% of ramipril. The extent of absorption is at least 50-60%. Food decreases the rate of absorption from the GI tract without affecting the extent of absorption. The absolute bioavailability of Ramipril and Ramiprilat were 28% and 44%, respectively, when oral administration was compared to intravenous administration. Lipids are considered as alternative to polymer in the design of controlled drug delivery systems due to their advantages like (a) low melt viscosity, thereby obviating the need of organic solvents for solubilization, (b) the absence of toxic impurities such as residual monomers catalyst and initiators, and (c) the potential biocompatibility and biodegradability and prevention of gastric irritation by forming a coat around the gastric irritatic drug . Among waxy materials, Gelucires are a mixtures of mono-, di-, and triglycerides and also poly(ethylene glycol) esters of fatty acid. Floating beads were formulated by using various materials like Gelucire (43/01,50/01), Tween 80, Oleic acid, Propylene glycol, Isopropyl alcohol, PG-400, DMSO, Methanol. A higher encapsulation efficiency of drug and percentage yield was obtained in formulations 11 that were 65.24±0.39 and 87.±0.26 due to higher Drug-Polymer ratio.The results indicated that the Thus, Gelucire 43/01 can be considered as an effective carrier for the design of a gastro retentive multiparticulates drug delivery system

Keywords: Ramipril, gastro retentive, intragastric floating tablets, floating drug delivery.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the Ease of administration, patient compliance and flexibility in formulation, etc. It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time(GRT).Dosage forms with a prolonged GRT, i.e. gastro retentive dosage forms (GRDFs), will provide us with new and important therapeutic options. GRDFs extend significantly the period of time over which the drug may be released. Thus, they not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs

Floating drug Delivery System:

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the

desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration.

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

Classification of Floating Drug Delivery System: 1,2,3.

A. Effervescent system

• Gas generating system

• Volatile liquid containing system

B. Non-effervescent System:

• Colloidal gel barrier system.

• Alginate beds.

• Hollow microspheres / Microballons.

• Intragastric Floating Drug Delivery Device / Microporous compartment system

A. Effervescent Systems:

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, C02 is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

a. Volatile liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid (like ether, cyclopentane), that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bio-erodible plug made up of PVA, Polyethylene, etc. that gradually dissolves and causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

b. Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. How the dosage form float is shown in the figure 4.

B. Non-effervescent systems:

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix

imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allow sustained release of drug through the gelatinous mass.

a. Colloidal gel barrier systems:1

Hydrodymamically balance system (HBSTM) was first design by Sheth and Tossounian in 1975.Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids.e.g.HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage form.

b. Alginate beads:

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours.

c. Hollow microspheres :2

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ehanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C.The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro.

d. Intragastric / Microporous compartment system:3

The system composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. The peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the undissolved drug with walls of the stomach.

MATERIALS AND METHODS

Ramipril IP was obtained as gift sample from Oniosome healthcare pvt. Ltd. Gelucire 43/01 & Gelucire 50/01 were received as gift samples from Gattefosse, Mumbai. Tween 80, Oleic acids was received as gift samples from Molychem Limited, Hyderabad. Propyleneglycol, Iso-propyl alcohol, Dimethyl sulfoxide was received as gift samples from Qualikems fine chem. Pvt. Ltd. Mumbai. Polyethylene glycol-400 was received as gift samples from SD Fine Chem. Ltd. Mumbai and all other chemicals/Solvents were procured from

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market are of analytical grade.

METHOD

Floating beads containing Ramipril were prepared by Lipid (Gelucire 43/01).Gelucire 43/01 was melted at 50°C, and the finely powdered drug was gradually added with uniform mixing to form dispersion. The resultant dispersion was dropped via a 23-guage syringe needle (0.65 mm internal diameter) into 100 ml of prechilled (4°C) IPA at a rate of 5ml/min. The distance from the needle tip to the IPA was 5 cm. The content was stirred at 100 rpm using magnetic stirrer for 15 min. The beads were collected after filtration through Whatman filter paper (# 41), washed three times with distilled.water, and subsequently dried to their constant weight in vacuum desiccator for 24 h to ensure complete removal of solvents. Beads were evaluated every 6 h for their weight. Various other vehicles such as Olive oil, light liquid paraffin, Ethanol, isopropyl myristate, Coconut oil and isopropyl alcohol separately and in different combination ratio were used as dispersion medium

RESULT & DISCUSSION

In the present investigation, a multiparticully system of Ramipril capable of providing controlled release was prepared using Gelucire 43/01. IPA is used as surface active agent and cross-linking agent. So might be these properties play an important role in uniform bead formation Schematic of preparation of beads. The method of preparation of beads was

Table 1: Composition of different formulations

S.No.	Formulation Code	Ramipril (mg)	Lipid	Amount of Lipid (mg)	Name of Solvent
1	F1	2.5	Gellucire 43/01	100	Isopropoanol
2	F2	2.5	Gellucire 50/13	100	Isopropoanol
3	F3	2.5	Compritol 888 AT	100	Isopropoanol
4	F4	2.5	Stearic Acid	100	Isopropoanol
5	F5	2.5	Gellucire 43/01	100	Ethanol
6	F6	2.5	Gellucire 43/01	100	light liquid paraffin
7	F7	2.5	Gellucire 43/01	100	Isopropyl myristate,
8	F8	2.5	Gellucire 43/01	100	Olive oil
9	F9	2.5	Gellucire 43/01	100	Coconut oil
10	F10	2.5	Gellucire 43/01	200	Isopropoanol
11	F11	2.5	Gellucire 43/01	300	Isopropoanol
12	F12	2.5	Gellucire 43/01	400	Isopropoanol
13	F13	2.5	Gellucire 43/01	500	Isopropoanol
14	F14	2.5	Gellucire 43/01	600	Isopropoanol

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Image of Gelucire floating beads

found to be simple and reproducible.

Before carrying out the formulation, preformulation studies on Ramipril were carried out, the results of which are described as below.

Preformulation Studies

Identification of Drug: The IR spectrum of pure drug was found to be similar to the reference standard IR spectrum of Ramipril.(Table 2)

Table 2: IR spectrum of pure drug

Characteristic peaks	Reported (cm^{-1})	Observed (cm^{-1})
Aromatic Ring	730-770	747.97
Aromatic Ring	690-710	697.03
C-O	1300-1000	1182.10
C-O Stretching	1700-1600	1646.08
C-H Stretching	3000-2850	2806.21

Table 3: Standard Calibration curveof Ramipril at 210 nm in pH 0.1 HCl

Conc.(µg/ml)	Absorbance
1	0.070± 0.001
2	0.099 ± 0.002
3	0.133± 0.003
4	0.165 ± 0.002
5	0.199 ± 0.001
6	0.235 ± 0.004
7	0.273± 0.002
8	0.303 ± 0.004
9	0340 ± 0.002
10	0.375 ± 0.002

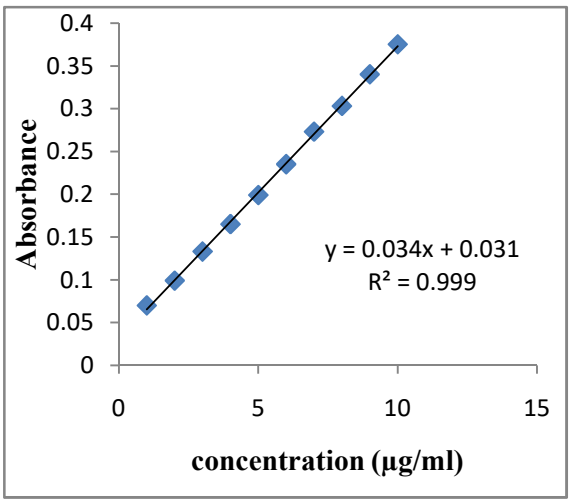

Fig. 1: Calibration Curve of Ramipril

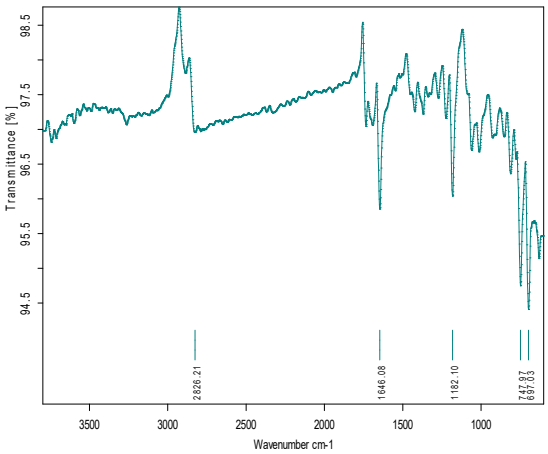

Fig 2: FTIR of Ramipril

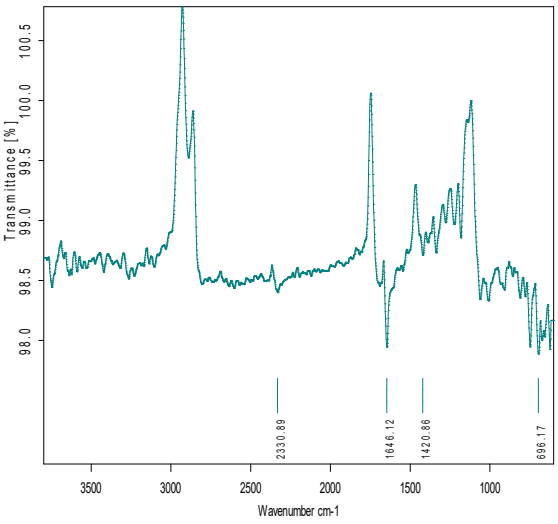

Fig 3: FT-IR spectrum of mixture of ramipril with Gelucire 43/01

Evaluation of beads

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Table 4: Appearance of different Gelucire

S.No.	Formulation Code	Appearance
1	F1	Threads like bead formed
2	F2	Less spherical bead formed
3	F3	Spherical Bead formed
4	F4	Spherical Beads formed
5	F5	Less spherical Beads formed
6	F6	Spherical Bead formed
7	F7	Less Spherical Bead formed
8	F8	Spherical Bead formed
9	F9	Spherical Bead formed
10	F10	Spherical Bead formed
11	F11	Spherical Bead formed
12	F12	Spherical Bead formed
13	F13	Spherical Bead formed
14	F14	Spherical Bead formed

Table 5: Percentage yield and Drug Entrapment

S.No.	Formulation Code	% Yield	%Drug Entrapment
1	F1	83 ±1.41	14.14 ±0.45
2	F2	92 ±2.3	25.74 ±1.11
3	F3	94.39 ±0.56	71 ±1.34
4	F4	88.69 ±0.33	46 ±0.58
5	F5	67.63 ±0.71	23.83 ±0.99
6	F6	65.2±0.41	45.23±0.31
7	F7	62.78±0.36	43±0.28
8	F8	60.57±0.34	41.93±0.32
9	F9	65.5±0.28	87±0.23
10	F10	65.49±0.23	65.49±0.25
11	F11	65.2	87±0.31
12	F12	62±.45	50.50
13	F13	62±0.33	36±1.11
14	F14	63±0.41	35±0.41

Table 6: Floating Lag Lime and Total Floating Time of Designed Formulations (F1 to F9)

Formulation Code	Floating lag time (Sec.)	Total Floating Time (hrs.)
F1	10.56	2
F2	12.52	3
F3	13.71	2
F4	10.47	2
F5	10.57	3.5
F6	10.67	3
F7	10.35	4
F8	10.36	4
F9	10.33	6.5
F10	10.28	5
F11	15.42	8
F12	11.23	6.5
F13	11.20	7

Table 7: Percentage In-vitro cumulative drug release of Formulation F11, Conventional tablet and pure drug

S.NO.	Time (hr)	% Cumulative drug release of F11	% Cumulative drug release of Conventional Tablet	% Cumulative drug release of pure drug
1	0	0±0	0±0	0±0
2	0.5	10.58±0.32	28.58±0.089	23.35±0.25
3	1	14.88±0.54	42.511±0.53	37.19±0.46
4	2	21.23±0.12	61.64±0.78	46.79±54

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5	3	28.70±0.059	76.57±0.80	53.37±0.71
6	4	36.15±0.027	86.18±0.60	78.66±0.31
7	5	43.61±0.31	95.77±0.62	92.55±0.54
8	6	54.24±0.11	96.88±0.57	94.74±0.80
9	7	62.77±0.83	97.94±0.99	95.81±0.95
10	8	70.22±0.47	97.95±0.53	96.88±0.67
11	9	78.74±0.29	99.011±0.004	97.94±0.78
12	10	86.2±0.25	99.017±0.51	99.011±0.54

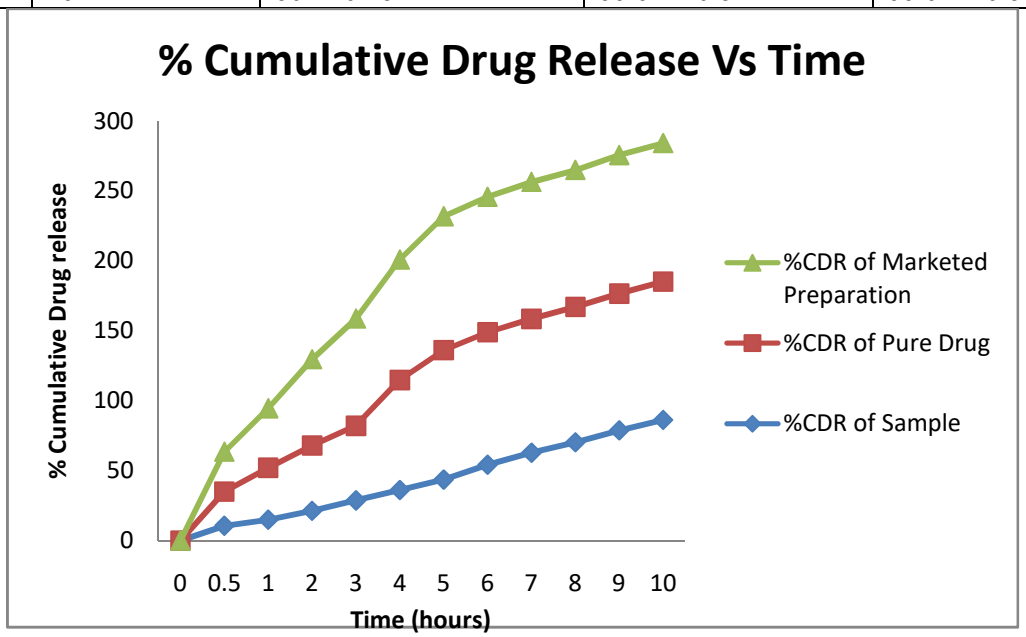

Fig:4 In-Vitro Cumulative Drug release of Ramipril loaded Gelucire floating beads, conventional tablet and pure drug

SUMMARY AND CONCLUSION:-

A higher encapsulation efficiency of drug and percentage yield was obtained in formulations 11 that were 65.24±0.39 and 87.±0.26 due to higher Drug-Polymer ratio. The results indicated formation of bead with different and reproducible size ranges, uniform shape and smooth outer surfaces. The different size of the produced spheres affects significantly the drug loading efficiency, the release profiles and the dose of the released drug. The size of F11 formulations was 1.90±01.80mm. The release profiles of Ramipril from beads made from Gelucire 43/01 showed that Gelucire 43/01 employed yielded a sustained Ramipril release. These behaviors can be explained in terms of release mechanism of the entrapped compound from the lipid beads. It has been suggested that, because of the high hydrophobicity of lipid materials, the release medium is not able to diffuse through the matrix and can progress in the dosage form by dissolving the grains of drug in contact with it. The dissolution of the drug particles on the surface of the matrix allows the formation of channels, from which the drug is slowly released.

According to model fitting methods the highest regression coefficient (R^2) value was 0.980 through Zero order. Hence from all aspects; we concluded

that the release of drug Ramipril can be controlled by proper designing of the formulation and selection of a suitable method of preparation.

It is concluded that the method of preparation of beads was found to be simple, reproducible, and provides good yield. The in vitro data obtained for floating beads of Ramipril showed excellent buoyancy ability. Prepared formulation showed better controlled release behavior when compared with its conventional dosage form and comparable release profile with pure drug Thus, Gelucire 43/01 can be considered as an effective carrier for the design of a gastroretentive multiparticulate drug delivery system.

REFERENCE

1. Sharma N, Agarwal D, Gupta M and Khinchi M. A comprehensive Review on Floating Drug Delivery System. Int J Res Pharm Biomed Sci. 2011;2: 428-41.

2. Klausner EA, Sara E, Lavy E, Friedman M, Hoffman A. Novel levodopa gastro-retentive dosage form: in-vivo evaluation in dogs. J. Control. Release, 2003; 88:117- 26.

3. Kale RD, Tayade PT. A multiple unit floating drug delivery system of Piroxicam using Eudragit polymer. Indian J PharmScie 2007; 69(1): 120-23.

4. Narang N. An updated review on: floating drug delivery system (FDDS). International Journal of Applied Pharmaceutics. 2011; 3, 01-07.

5. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000; 63:235-59.

6. http://www.pharmpedia.com/images/d/d7/Neelam.pdf

7. Arunachalam A, Karthikeyan M, Konam K, Prasad PH, Sethuraman S, kumar SA, Manidipa S. Floating drug delivery systems: A review. Int. J. Res. Pharm. Sci. 2011; 2(1):76-83.

8. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review.AAPS Pharm Sci Tech 2005; 6 (3) Article 47: E372–E390.

9. Shahaa SH, Patelb JK, Pundarikakshudua K, Patel NV. An overview of a gastro- retentive floating drug delivery system. Asian Journal of Pharmaceutical Sciences. 2009; 4 (1): 65-80.