AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation and Evaluation of Controlled Release Floating Tablet of Perindopril Erbumine using Natural Polymer

Balkrushna K. Patel [1*], Paresh U. Patel [2]

1.K.J.College of Pharmacy, At & Post Vadasma, Ta.& Dist. Mehsana, Gujarat, India

2. SKPCPER, Ganpat University, Ganpat Vidhyanagar, Mehsana, Gujarat, India.

ABSTRACT

Floating dosage form for gastric retention has potential to use as controlled-release drug delivery systems which providing opportunity for both local and systemic drug action. The present work was aimed to formulate controlled release floating tablet (CRFT) of Perindopril Erbumine using gas generated low density approach. To develop CRFT, the Perindopril Erbumine was selected as a drug because it complies with the suitability criteria for the floating drug delivery system and the controlled release medication was required due to its potent action and poor bioavailability. The present investigation was suggested that the bioavailability of Perindopril Erbumine was improved due to increased gastric retention time and controlling the drug release rate using the natural polymer SFG, HPMCK15M and Acrypol 934. The CRFT of Perindopril Erbumine was developed by using wet granulation method and PVP K 30 was used as a granulating agent. The study was given the assurance that SFG had an excellent controlled drug releasing property then HPMCK15M by forming matrix in the formulation. The Acrypol 934 was added to control the drug release rate in to formulation and found good compressibility and controllable drug releasing properties in to the final formulation. All the formulation was evaluated for Weight variation, Thickness, Hardness, Diameter, Friability, Assay, FLT, TFT, Swelling Index and Dissolution study.

Key Word: CRFT, SFG, Acrypol 934, FLT, TFT, SWI, Perindopril Erbumine, DSC

*Corresponding Author Email:balu.pharma22@gmail.com

Received 08 October 2012, Accepted 13 October 2012

Please cite this article in press as: Patel B. *et al.*, Formulation and Evaluation of Controlled Release Floating Tablet of Perindopril Erbumine using Natural Polymer American Journal of PharmTech Research 2012.

INTRODUCTION

For the present study, the aim was to develop controlled release foating dosage form to increase the gastric residence time for the drug which leads to increase the bioavailability of drug. Many literatures were suggested that the most convenient method of controlled delivery of drug is undoubtedly oral, but oral controlled release of the drug for an extended period of time that exhibits more absorption in stomach and upper small intestine, has not been successful with conventional approaches. So, it has been decided to develop the controlled release floating dosage form as a novel approach for the drug delivery and the tablet is well known as most convenient dosage form among all oral drug delivery. Finally it was decided that to develop a controlled release floating tablets (CRFT). These systems are also called as hydrodynamically balance systems (HBS). It is an oral dosage form designed to prolong the residence time of the dosage form within the gastrointestinal track. To provide good floating behavior in the stomach, the density of the floating drug delivery system (FDDS) should be less than that of gastric content (< 1.0049 g/cm^3).

The various types of buoyant preparations include hollow microspheres, granules, powders, capsules, tablets, cylinders and laminated films. Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS, which are effervescent systems and non-effervescent systems.[1, 2]

The gastric retention time (GRT) of dosage forms is controlled by several factors, such as density of the dosage form, size of the dosage form, food intake, nature of the food, posture of the host, age, sex, sleep and disease state of the individual (e.g. gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents. [3-7]

One of the major disadvantages of floating system is the requirement of high level of fluid in the stomach for the delivery system to float and work efficiently. This system also requires the presence of food to delay their gastric emptying. In addition, there are limitations to the applicability of floating system for drugs that have the high solubility or solubility problem in highly acidic gastric environment or that irritant to gastric mucosa. Drugs, which are well absorbed along the entire GI tract and undergo significant first pass metabolism may not be desirable candidates for formulation as GRDFs since the slow gastric emptying may lead to reduced systemic bioavailability. So the drug candidate that can be choosing for such dosage forms should have any of the following characteristics.

- ***Narrow absorption window in GI tract***
- ***Primarily absorbed from stomach***
- Poorly soluble at higher pH
- Higher solubility at acidic pH
- ***Act locally in stomach***
- ***Degraded in colon***

Perindopril Erbumine is a novel antihypertensive agent, widely absorbed from the stomach and upper part of the small intestine. It has shorter elimination half life (0.8hr to 1hr), so necessity to frequent administration and bioavailability can be improved by making the drug completely absorbed in the stomach and upper part of the small intestine.

CRFT of Perindopril Erbumine was developed using sterculia foetida gum (SFG). SFG is a natural gum and it is obtained from gummy extrudes from stem bark of sterculia foetida belongs to the family of sterculiaceae. It is freely soluble in water via hydration and practically insoluble in absolute ethanol. It is used as suspending agent, viscosity enhancer and rate controlling polymer in controlled release dosage.

MATERIALS AND METHODS

Perindopril Erbumine was obtained as a gift sample from Zydus Cadila Healthcare limited, Ahmedabad. Sterculia Foetida Gum (SFG) was obtained as a gift sample by Medicinal natural products research laboratory, University Institute of Chemical Technology, Mumbai. HPMC K 15 M and PVP K 30 obtained as a gift sample from Alembic limited, Vadodara. Acrypol 934 was obtained as gift sample from Corel Pharma Chem, Ahmedabad. $NaHCO_3$, Lactose, Talc, Mg. Stearate and IPA used in the present study were provided by K. J. College of pharmacy, Vadasma, Gujarat. India.

Compatibility Study

FTIR [8, 9]

The pure drug i.e. Perindopril Erbumine and the mixture of drug with various polymers used in the preparation of floating tablet formulations were analysed by FT-IR spectroscopy to know the compatibility with each other. The FTIR spectra were taken on a Shimadzu (FTIR-8300) instrument for all samples and it was measured by KBr disk method. It was shown in Figure 1.

DSC [8, 9]

The pure drug i.e. Perindopril Erbumine and the mixture of drug with various polymers used in the preparation of floating tablet formulations were also measured by DSC to study about the

physicochemical compatibility with each other. Thermograms of the drug alone and drug - polymer physical mixture were obtained from a Shimadzu (DSC- 60) instrument. The instrument was calibrated with an indium standard. The samples (2-4 mg) were heated over a temperature range of (50-300°C) at a constant scanning speed (10°C/min) in sealed aluminum pans, using nitrogen as purging gas at a rate of 20 ml/min. It was shown in Figure 2.

Preparation of Perindopril Erbumine Floating Tablet

Perindopril Erbumine controlled release floating tablets were prepared by wet granulation techniques using different concentrations of various polymers. To prepare tablet, weighed all ingredients except talc and magnesium stearate and shifted through sieve no 40 then blend uniformly in glass mortar with pestle. After sufficient mixing, the blend was wetted by adding sufficient quantity of isopropyl alcohol as a granulating agent. Prepared wet mass was granulated by passing through sieve no 18. Prepared granules were dried at 50 ^{0}C – 60 ^{0}C for 20 min in hot air oven. After drying, dried granules were lubricated by adding sufficient quantity of magnesium stearate and talc for 5 min. Then, the granules were ready for compression. The tablets were compressed using 6 mm punch on 8 station rotary punching machine.

Evaluation of Perindopril Erbumine CRFT [9]

Weight variation

Twenty tablets were randomly selected from each formulation and individually weighed in milligrams. The average weight and standard deviation of 20 tablets was calculated. The values of average weight and standard deviation of the tablets of each formulation are given in Table 2.

Thickness

Twenty tablets were randomly selected from each formulation and measured thickness in millimeter of each tablet by Vernier Calliper. The standard deviation was calculated from the average thickness and it is shown in Table 2.

Diameter

Twenty tablets were randomly selected from each formulation and measured diameter in millimeter of each tablet by Vernier Calliper. The standard deviation was calculated from the average diameter and it is shown in Table 2.

Hardness

Twenty tablets were randomly selected from each formulation and measured hardness in kg/cm^2 using Monsanto type hardness tester. The standard deviation was calculated form average hardness and it is shown in **Table 2**.

Friability

Twenty tablets were randomly selected from each formulation and after weighing accurately placed in the electrolab friabilator. The rotation speed of friabilator was kept at 20 rpm for 5 minute. After 5 minutes, the tablets were dedusted and weighed again. The percentage friability is measured using the formula,

$$\textbf{Percentage of Friability (\% F)} = [1 - (W/W_0)] \times 100$$

Where,

W_0 = Initial weight of tablets (g)

W = Final weight of tablets after rotation (g)

The results of measured percentage friability are shown in Table 2.

Assay

10 tablets were randomly selected from each formulation and crushed to a fine powder in mortar with pestle. Weigh accurately equivalent to 8 mg of Perindopril Erbumine from fine powder then transfer in 100 ml volumetric flask, 100 ml of 0.1 N HCL was added to dissolve and sonicated for 20 minutes. After Sonication, insoluble matter was allowed to settle. The resultant solution was diluted to get concentration about 8.5 µg/ml Perindopril Erbumine in 0.1 N HCL. Resulting solution was filtered through whatman filter paper. Absorbance of final resultant solution was measured in U V Spectrophotometer at 207 nm. The concentration of drug present in final diluted solution was calculated from the calibration plot of Perindopril Erbumine in 0.1 N HCL and find out actual drug content present in it. The value of drug content present in tablets of each formulation is shown in Table 2.

Floating Properties [10]

To measure the floating properties, five tablets from each formulation were selected randomly and placed in beaker containing 250 ml of 0.1 N HCL (pH 1.2). The temperature was maintained at 37 ± 0.5 ^{0}C. The time by which the tablet started to float on the surface of medium for FLT and entire duration of time by which the tablet constantly remained on the surface of the medium for TFT was noted. The Floating lag time (FLT) and Total Floating Time (TFT) of tablet of each formulation is shown in Table 2**.**

5.5.8 Swelling Study [10]

The extent of swelling can be measured in terms of percentage weight gain by the tablet. Five tablets from each formulation were selected randomly for the swelling study. Each tablet individually weighed (W_0) and separately placed in beaker containing 100 ml of 0.1N HCL (pH 1.2). The tablet was removed from each beaker after 1 hour of time interval and excess surface

solvent from the tablet was wiped out carefully with filter paper. Each swollen tablet was reweighed (W_t) and the swelling index (SI) is calculated using the following formula,

$$\textbf{Swelling index (SI)} = [(W_t - W_o) / W_o] \times 100$$

Where,

W_t = Final weight of tablet at time t (mg)

W_o= Initial weight of tablet (mg)

The value of swelling index for the tablet of each formulation was given in Table 3.

In Vitro Dissolution Study [11]

The *In-vitro* dissolution study for the tablet of each formulation was conducted as per United States Pharmacopoeia type II apparatus. The rotating paddle method was used to study the drug release from the tablets. Dissolution medium 900 ml of 0.1 N HCl (pH 1.2) was placed in dissolution vessel. The release was performed at 37 ^{0}C ± 0.5 ^{0}C and at a rotational speed of paddle about 50 rpm. Tablets were placed in each dissolution vessel. The 5 ml samples were withdrawn at the time interval of one hour for 16 hrs. The collected samples were filtered through Whatman filter paper No. 40 and analyzed for drug content by UV Spectrophotometer. The absorbance for each sample was measured at 207 nm and the concentration of drug present was calculated using calibration plot of Perindopril Erbumine. Then, the cumulative percentage amount of drug released at each time interval was calculated using the formula,

$$\textbf{Cumulative amount of drug release} = C \times DF \times DM$$

Where,

C = Concentration of drug at each time interval (µg/ml)

DF = Dilution Factor is 1.

DM = Dissolution Medium (900 ml)

The in vitro release profiles of Perindopril Erbumine from each formulation are shown in Table 4 and represented in Figure 3.

RESULTS AND DISCUSSION

SFG and HPMC were selected as a matrix forming agent considering its widespread applicability and excellent gelling activity in controlled release formulations. Sodium bicarbonate was used to generate CO2 gas in the presence of hydrochloric acid present in dissolution medium. The generated gas was trapped within the gel formed by hydration of metrix forming polymers, thus decreasing the density of the tablet. Acrypol 934 was used as cross linking agent which helps to maintain gel matrix for longer period of time. As the density of tablet reduce, the tablet becomes

buoyant when the density below 1. Six batches F1 to F6 prepared by using different composition which is shown in Table 1. The evaluation parameters diameter, friability, buoyancy time, weight variation of all the formulation shown in Table 2. Lowest FLT was observed in formulation F5 which was 80 seconds.

Table 1: The Composition of Perindopril Erbumine CRFT

Ingredient	F1	F2	F3	F4	F5	F6
Drug	8	8	8	8	8	8
SFG	12	16	--	--	10	--
HPMC K15M	--	--	12	16	--	10
Acrypol 934	--	--	--	--	6	6
$NaHCO_3$	10	10	10	10	10	10
PVP K 30	5	5	5	5	5	5
Lactose	45	41	45	41	41	41
Talc	2	2	2	2	2	2
Mg. Stearate	3	3	3	3	3	3
IPA	qs	qs	qs	qs	qs	qs
Total	**85**	**85**	**85**	**85**	**85**	**85**

Note: - All the values were in mg per tablet

Swelling study was performed for all the formulation up to 16 hr. Maximum swelling was observed in formulation F5 which was 99.34 % after 16 hr. It was indicated that the mixture of SFG and Acrypol 934 produce stable gel matrix upon hydration. And swelling was increased due to the expansion of gel matrix by trapping generated CO_2 gas.

Table 2: Physical Evaluation of Perindopril Erbumine CRFT

Code	AW ± SD n = 20	H ± SD n = 20	T ± SD n = 20	D ± SD n = 20	Friability(%)	FLT	TFT	Assay
F1	85.34±1.38	5.60±0.29	3.05 ±0.14	5.96±0.07	0.195	80	>12	99.93
F2	85.13±1.37	5.65±0.20	3.00 ±0.11	5.95±0.04	0.152	83	>16	99.47
F3	85.06±1.07	5.55±0.15	3.05 ±0.12	5.92±0.05	0.291	91	>12	98.17
F4	84.40±1.16	5.65±0.10	3.00 ±0.11	5.91±0.05	0.278	95	>16	99.01
F5	85.9±1.36	5.95±0.21	3.05 ±0.10	5.90±0.05	0.033	80	>16	99.97
F6	84.0±1.05	5.75±0.07	2.95±0.05	5.90±0.05	0.171	87	>15	98.97

Note: AW = Average Weight (mg), H = Hardness (kg/cm^2), T = Thickness (mm), D = Diameter(mm), FLT = Floating Lag Time (Seconds), TFT = Total Floating Time (Hours)

Table 3: % SWI of Perindopril Erbumine CRFT

Code	% Swelling Index , n = 5									
	1(hr)	2(hr)	3(hr)	4(hr)	6(hr)	8(hr)	10(hr)	12(hr)	14(hr)	16(hr)
F1	22.80	34.60	46.20	53.70	65.90	76.00	83.15	85.96	88.21	89.08
F2	29.70	42.10	53.80	64.60	73.20	82.90	87.19	90.28	91.99	92.29
F3	20.3	31.7	42.1	51.5	62.9	71.1	78.18	80.96	82.89	83.18
F4	25.2	38.8	48.8	57.7	68.3	76.9	83.64	86.48	88.29	89.13
F5	28.7	43.4	55.9	66.9	76.7	88.1	93.93	96.89	97.99	99.34
F6	25.2	38.9	51.8	63.9	74.9	82.5	85.90	88.89	89.09	89.38

The results of in vitro drug release study from the Perindopril Erbumine CRFT and it was shown in Table 4. From the result, it was indicated that the drug release rate was decreased as the concentration of polymer increased. The effect of drug release with time was shown in Figure 1, Formulation F5 was observed as more controllable drug release then other formulations. The similarity value of all the formulation was also indicated that Formulation F5 was shown similar dissolution profile with theoretical drug release profile.

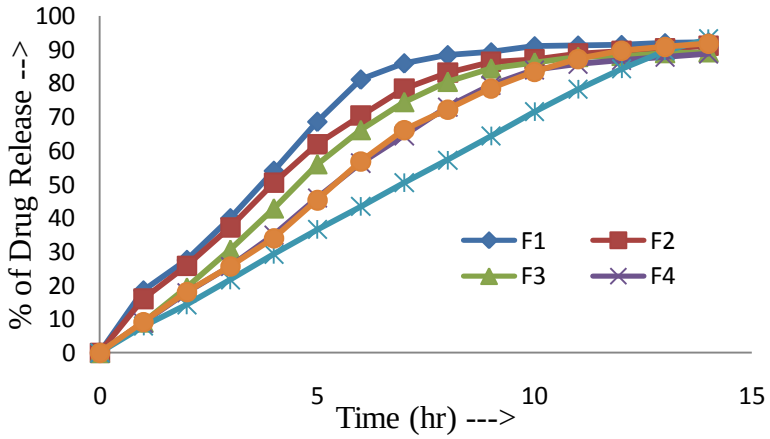

Figure 1: Drug release profile from Perindopril Erbumine CRFT

Table 4: Cumulative % of Drug Release of Perindopril Erbumine CRFT

Time (hr)	% of Drug Release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
1	18.49	16.02	09.02	08.83	07.88	09.02
2	27.54	25.81	19.37	17.82	14.25	17.96
3	39.91	37.21	30.55	25.69	21.63	25.64
4	53.98	50.42	42.82	34.95	29.25	34.03
5	68.54	61.82	55.91	46.03	36.55	45.28
6	81.06	70.25	66.02	56.29	43.39	56.73
7	85.86	78.32	74.32	64.38	50.38	66.08
8	88.28	83.08	80.32	72.88	57.08	72.19
9	89.11	86.29	84.29	79.38	64.28	78.43
10	90.91	87.02	86.07	83.92	71.42	83.31
11	91.12	88.71	87.68	85.65	78.05	87.08
12	91.28	89.48	88.01	86.72	84.19	89.64
13	91.81	90.22	88.83	87.81	89.51	90.81
14	92.05	90.97	89.08	88.67	93.07	91.68
Similarity Factor (F2)	**29.40**	**33.52**	**37.22**	**44.67**	**70.26**	**44.35**

In vitro drug release profiles follow the korsemeyer and peppas model to release the drug. It was shown in Table 5. It was indicated that drug release pattern from the swelling and erodible diffusion matrix for the developed formulation because the value of n was greater than 0.89. The

drug release mechanism follows the zero order release which is shown in Table 5. Formulation F5 shows more controllable release among all the formulation.

Table 5: Drug release kinetic data derived from various kinetic models

Code	Zero Order		First Order		Hixon Crowell		Korsemeyer Peppas			Higuchi Plot	
	(R^2)	K_0	(R^2)	K_1	(R^2)	K_H	(R^2)	n	K_k	(R^2)	Kp
F1	0.9718	7.0361	0.7862	0.2277	0.9040	0.5954	0.9844	0.7951	1.6534	0.9820	0.0335
F2	0.9930	7.0397	0.8416	0.2450	0.9450	0.6204	0.9974	0.9255	1.0929	0.9703	0.0338
F3	0.9537	7.2879	0.7932	0.2390	0.8943	0.6191	0.9836	0.9101	1.3620	0.9730	0.0314
F4	0.9781	7.3125	0.8216	0.2445	0.9247	0.6291	0.9940	0.9354	1.1876	0.9739	0.0321
F5	0.9996	6.9659	0.8557	0.2496	0.9564	0.6225	0.9996	0.9670	0.9534	0.9654	0.0342
F6	0.9834	7.4840	0.8255	0.2462	0.9304	0.6380	0.9950	0.9388	1.1871	0.9744	0.0316

FTIR spectra of all the samples conformed that there was no interaction between drug and excipients used and it is shown in Figure2. DSC thermograms of all the samples also suggested that there was no interaction between drug and excipients used and it is shown in Figure 3.

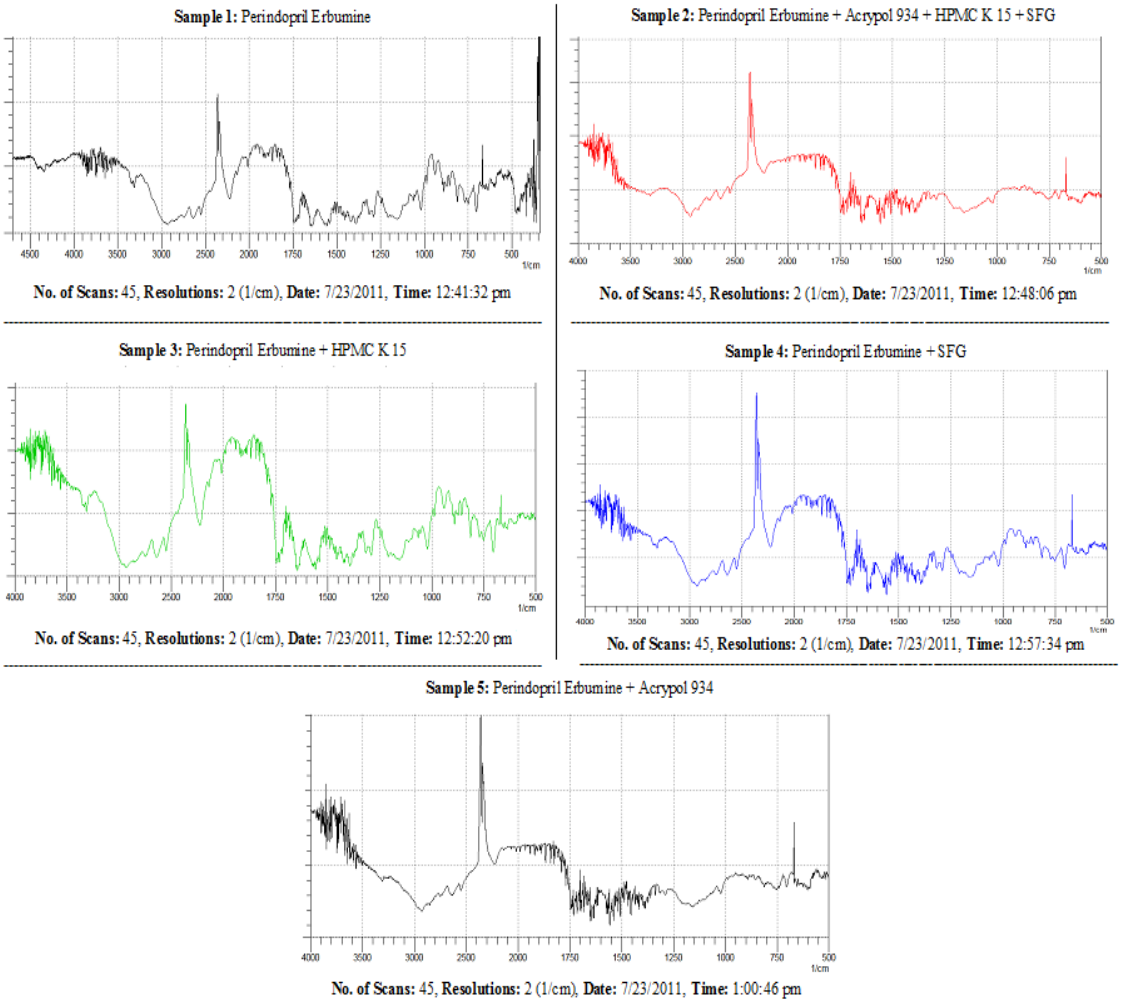

Figure 2: FTIR Spectra for Compatibility Study

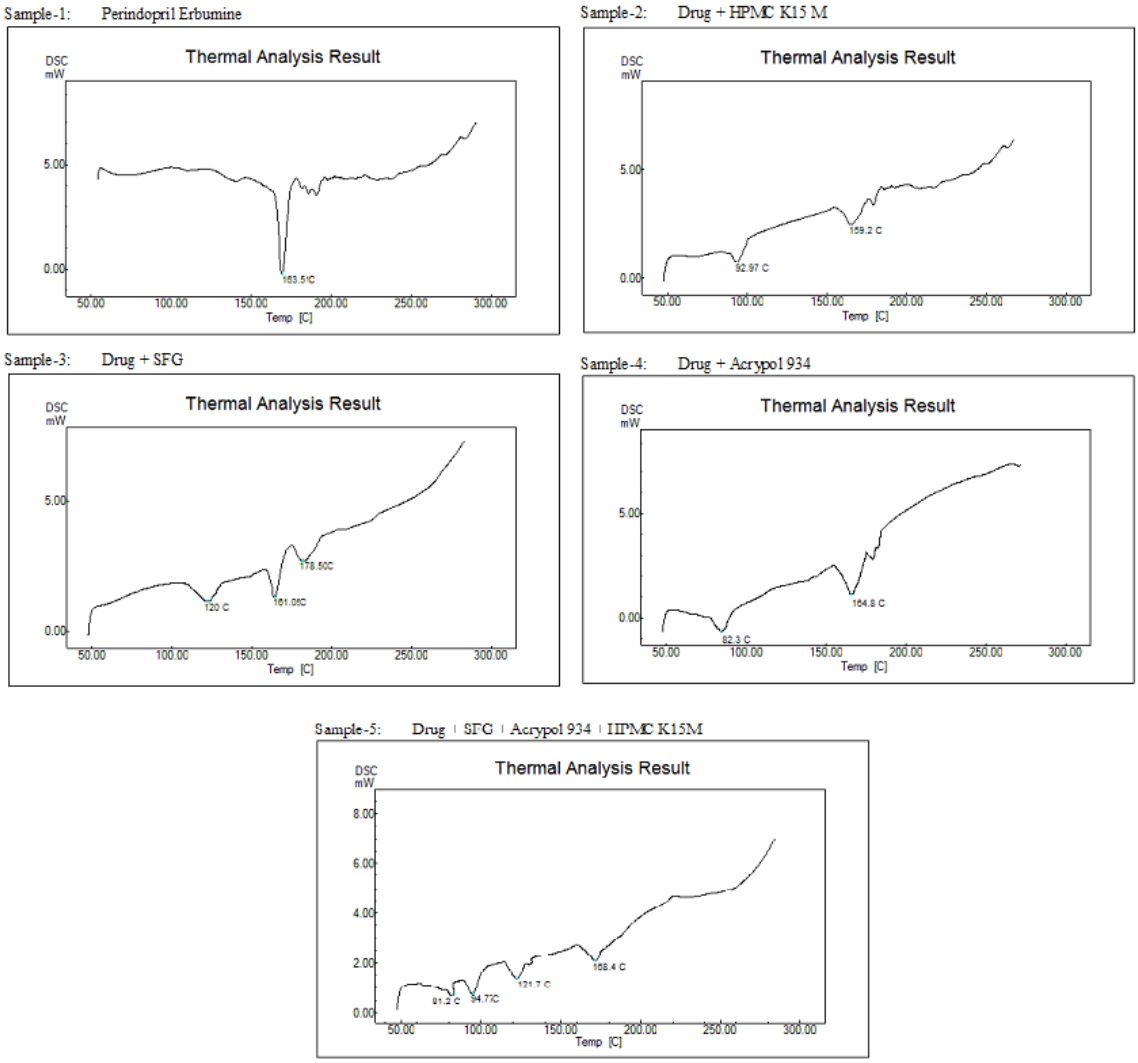

Figure 3: DSC thermograms for Compatibility Study

CONCLUSION

The present study was aimed to develop an oral controlled release floating tablet for Perindopril Erbumine with the use of swellable natural polymers and t was compared with swellable synthetic polymer. It released the drug in a controlled manner for extended period of time by maintaining the buoyancy for more than 16 hr with very short lag time. In vitro release data were fitted to various kinetic models and drug release predominantly followed non-Fickian diffusion from the swelling matrix and near to zero order mechanism for formulation F5. Overall, this study concludes that viscosity of polymer is a major factor affecting the drug release and floating properties of developed CRFT.

REFERENCE

1. Vyas SP, Khar RK. Gastroretentive system, Controlled Drug Delivery- Concepts and

advances. In: 1st edition. 2002: 196-217

2. Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for floating drug delivery system: effects of CO_2 gas-forming agents. Int J Pharma 2002; 239: 81-91.
3. Bechgaard H, Christensen FN, Davis SS, Hardy JG, Taylor M J, Whalley DG, Gastrointestinal transit of pellet systems in ileostomy subjects and the effects of density. J Pharm Pharmacol 1985; 37: 718-721.
4. Sangekar W, Vadino WA, Chaudry I, Parr A, Beihn R, Digenis G. Evaluation of the effect of food and specific gravity of tablets on gastric retention time. Int J Pharma 1987; 35: 187-191.
5. Coupe AJ, Davis SS, Evans DF, Wlding IR. Correlation of gastric emptying of non-disintegrating tablets with gastrointestinal motility. Pharma Res 1991; 8: 1281-1285.
6. El-kamel AH, Sokar MS, Al-gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharma 2001; 220:13-21.
7. Mojaverian P, Vlasses PH, Kellner PE, Rocci ML. Effects of gender, posture and age on gastric residence time of an indigestible solid: Pharmaceutical consideration. Pharm Res 1988; 10: 639-644.
8. Gilbert S, Banker, Anderson. The Theory and Practice of Industrial Pharmacy. Leon Lachman. In: 3rd edition. p 318-319.
9. Patel VF, Patel NM, Yeole PG. Studies on formulation evaluation of ranitidine floating tablet. Ind J Pharm Sci 2005; 67: 703-709.
10. Dave BS, Amin AF, Patel MM. Gastroretentive Drug delivery system of Ranitidine Hydrochloride: Formulation and In vitro evaluation. AAPS. 2004; 5: 1-6.
11. Pillay V, Fasihi R. Evaluation and comparison of dissolution data derived from different dosage forms: An alternative method. J Contol Release. 1998; 55: 45-55.