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Formulation and evaluation of floating drug delivery system containing theophylline as a model drug

Vipul Chaudhari*, Hetangi Rathod and Moin Modasia
APMC College of Pharmaceutical Education and Research, Himatnagr - India

Abstract

The objective of this research work was to formulate and evaluate the floating drug delivery system containing theophylline as a model and to optimize the drug release profile. Theophylline tablets were prepared by direct compression. Formulations contain HPMC K100M, xanthan gum, carbopol 934P, PVP K30, MCC, lactose, aerosil and gas generating agent such as sodium bicarbonate were taken as independent variables. The effect of formulation variables on floating and drug release was evaluated. The release mechanisms of theophylline from floating tablet where evaluated on the basis of Peppas model.

Key-Words: Floating drug delivery systems (FDDS), Compatibility, FT-IR

Introduction

Oral route is the most convenient and extensively used route for drug administration. This route has high patient acceptability, primarily due to easy of administration.[1] Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes. Most of the oral controlled drug delivery systems rely on diffusion, dissolution or combination of both mechanisms, to release the drug in a controlled manner to the Gastrointestinal Tract (GIT) and the drug profile data, such as dose, absorption properties and the quantity of drug needed, one can determine the desired release rate of the drug from controlled release dosage form.[2]

Drugs that are easily absorbed from the G.I.T and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem the oral controlled release formulations have been developed, as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time.[3]

*** Corresponding Author:**
E-mail: het_pharma277@yahoo.co.in

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of the body, to achieve promptly and then maintain the desired therapeutic drug concentration that elicits the pharmacological action and to minimize the incidence and the severity of unwanted adverse effects. To achieve this goal, it would be advantageous and more convenient to maintain a dosing frequency to once, or at most, a twice-daily regimen. An appropriately designed extended release dosage form can be a major advance in this direction.[5]

Many attempts have been made to develop sustained-release preparations with extended clinical effects and reduced dosing frequency. In order to develop oral drug delivery systems, it is necessary to optimize both the release rate of the drug from the system and the residence time of the system within the gastrointestinal tract.[6]

The present investigation concerns the development of the floating matrix tablets, which after oral administration are designed to prolong the gastric residence time, Increase the drug bioavailability, diminish the side effects of irritating drugs. [7]

To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents.

Material and Methods

Collection of plant materials

Theophylline was a gift sample from Eros Pharma Pvt. Ltd, Bangalore India. HPMC (K100M), Xanthan gum, Carbopol 934P And Aerosil were obtained from Strides

Arco labs Pvt. Ltd, Bangalore. All other reagents and chemicals used were of analytical reagent grade.

Preparation of floating tablets

The drug and excipients were passed through an 85 # size mesh prior to the preparation of the dosage form. The entire ingredient are weighed separately and mixed thoroughly for 10 mints to ensuring uniform mixing in geometrical ratio. The tablets are prepared by direct compression method by using Rimek RSB-4, Minipress.

Evaluation of the tablet

***In vitro* floating study:**

The in vitro floating behavior of the tablets was studied by placing them in 900 ml of plastic containers filled with 500 ml of 0.1 N HCl. (pH 1.2, 37 ± 0.5°C). The floating lag times (time period between placing the tablet in the medium and tablet floating) and floating durations of the tablets were determined by visual observation. The floating lag time were given in this table 1.

***In vitro* dissolution study**

The release rate constant and diffusion coefficient are obtained after fitting the release rate data to zero order, first order and Krosmeyer and Peppas model. The multiple regression analysis was done using DESIN EXPERT 6.05 (STAT-EASE), which is specially meant for this optimization process. The result of this analysis is presented in the table no 2. [8]

Scanning Electron Microscopy (S.E.M)

The surface morphology of pure materials, their treated counterparts, and all binary systems were examined by scanning electron microscope. The samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. The pictures were taken at an excitation voltage of 20 Kv. JSM-840A Scanning Microscope, Jeol-Japan with JFC-1100E Ion Sputtering Device was used.

Results and Conclusion

An attempt was made to formulate and evaluate floating drug delivery system containing theophylline as a model drug, because theophylline, a methyl xanthine derivative used in the treatment of chronic asthma as an adjunct to β_2 agonist and corticosteroid therapy. It is rapidly absorbed after oral administration with a half-life of 4 – 8 hr's and no difference in the amount of absorption between the stomach, ileum & colon. Hence the floating form was developed. However, it is prepared by direct compression method. Direct compression method of theophylline tablet containing HPMC (K100M), xanthan gum, carbopol 934P, aerosil and sodium bicarbonate, PVP K30, lactose and MCC.

Scanning electron microscopic (S.E.M)

The topography of dry tablet (Figure 2), its surface is showing non-uniformity with membrane structure the pores and drug particles where as wet and dry tablet surface shows that drug and excipients particles and also shows the membrane like gel structure. The images of the dry tablet surface showed a degree of mechanical interlocking of the tablet excipients particles. Structure of sectioned tablet before wet shows non-uniformity gel structure with pores and structure of tablet after wetting shows that well formed gel with less number of pores by the polymer relaxation upon absorption of water.

Differential scanning calorimetry (DSC) studies:

Individual coils that are heated and cooled at the same rate heat DSC in which sample and reference containers are not contiguous and heated them separately. Platinum resistance thermometers monitor the temperature of the sample and reference holders and electronically maintain the temperature of the two holders constant. For thermal analysis of drug and drug-excipients mixtures, a differential scanning calorimeter (DSC) (Perkin-Elmer, DSC-2) was used. Individual samples (drug and selected excipients (all passed through sieve 60-mesh) were weighed directly in the pierced DSC aluminum pan and scanned in the temperature range of 50-300 ^{O}C (at the heating rate of 10 ^{O} C / min.) under an atmosphere of dry nitrogen. DSC are shown in figure 4-14.

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Table : Ingredients used in the formulation of tablets with their composition

S/No.	Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Theophylline	100	100	100	100	100	100	100	100	100	100	100	100
2	HPMC (K100M)	100	100	50	100	100	100	50	50	50	100	50	50
3	Xanthan gum	-	50	50	-	50	50	50	-	-	-	50	-
4	Carbopol 934P	50	-	50	50	-	50	50	50	-	-	-	-
5	Aerosil	10	30	10	30	30	10	30	30	30	10	10	10
6	PVP (K30)	40	40	-	40	-	-	40	-	-	-	40	40
7	MCC	-	-	40	-	40	40	-	40	40	40	-	-
8	$NaHCO_3$	-	-	-	40	-	40	40	-	40	40	40	-
9	DCP	35	-	-	-	35	-	35	35	-	35	35	-
10	Lactose	-	35	35	35	-	35	-	-	35	-	-	35
11	Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5
12	Talc	10	10	10	10	10	10	10	10	10	10	10	10
TOTAL (mg)		350	370	350	410	370	440	410	320	310	340	340	250

All the ingredients are in mg. per tablet.

Note: HPMC (Hydroxy propyl methyl cellulose), MCC (Microcrystalline Cellulose), $NaHCO_3$ (Sodium bicarbonate), and PVP (Poly-vinyl Pyrrolidone), DCP (Dibasic calcium Phosphate).

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Table 1: Evaluation parameter of floating tablet

Formulation	% Drug Content	Floating lag time
F1	106.91	-
F2	105.21	-
F3	107.9	-
F4	106.69	5 min
F5	104.17	-
F6	102.63	-
F7	103.86	-
F8	101.93	-
F9	102.77	1 sec
F10	100.05	5 sec
F11	100.7	2 sec
F12	99.05	-

Table 2: Cumulative drug release study of drug

Time (Hrs)	% Cumulative drug release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	15.35	15.83	13.83	10.74	15.59	15.43	13.51	19.41	17.61	10.81	4.061	21.62
2	27.49	25.13	23.47	18.42	24.42	25.77	17.44	23.99	20.07	20.95	11.94	35.41
3	36.54	32.22	31.77	24.53	31.08	33.90	26.95	38.06	29.20	30.65	18.59	47.44
4	45.35	37.10	39.06	30.14	37.12	41.98	39.09	49.20	35.32	37.63	24.47	56.26
5	50.95	41.92	39.51	35.44	44.04	49.27	39.98	53.81	41.35	44.82	29.54	65.46
6	54.84	48.13	45.53	40.35	45.78	54.79	50.58	62.24	50.44	50.63	33.25	71.19
7	61.56	51.44	49.77	43.56	52.70	58.38	50.37	65.38	51.53	54.80	39.75	79.55
8	66.68	55.32	53.47	47.39	56.33	65.99	53.83	63.73	53.78	64.47	44.01	83.93

Table 3: Release kinetic study of drug from floating tablets

Batch	Model							
	Higuchi		Zero order		Peppas		First order	
	k	R^2	k	R^2	k	R^2	k	R^2
F1	17.84	0.9488	7.45	0.8573	13.67	0.9914	0.10	0.9721
F2	19.04	0.9841	7.9	0.7371	16.66	0.9981	0.11	0.9277
F3	18.42	0.9695.	7.64	0.7388	15.95	0.9851	0.10	0.9211
F4	15.75	0.9439	6.59	0.8920	11.53	0.9978	0.08	0.9773
F5	19.15	0.9731	7.96	0.7901	15.98	0.9963	0.11	0.9489
F6	24.67	0.9500	9.05	0.8746	16.31	0.9970	0.13	0.9900
F7	18.38	0.9027	7.70	0.8727	13.09	0.9618	0.10	0.9620
F8	21.87	0.9318	9.1	0.7593	18.13	0.9557	0.13	0.9477
F9	18.66	0.9415	7.78	0.8099	14.91	0.9735	0.10	0.9408
F10	17.98	0.8831	7.61	0.9681	10.54	0.9936	0.11	0.9942
F11	13.31	0.8334	5.68	0.9905	6.38	0.9930	0.07	0.9908
F12	17.15	0.84	7.6	0.8725	8.12	0.9322	0.13	0.976

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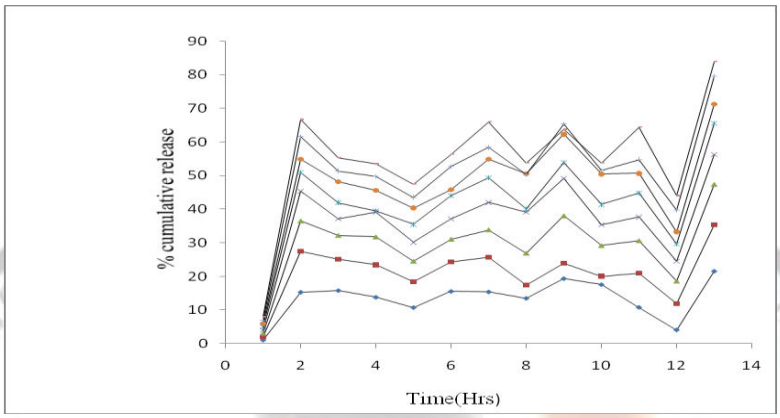
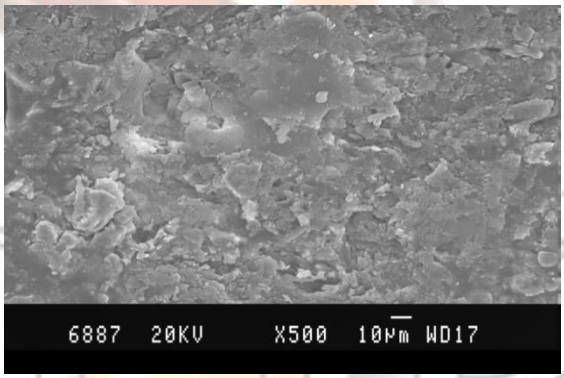
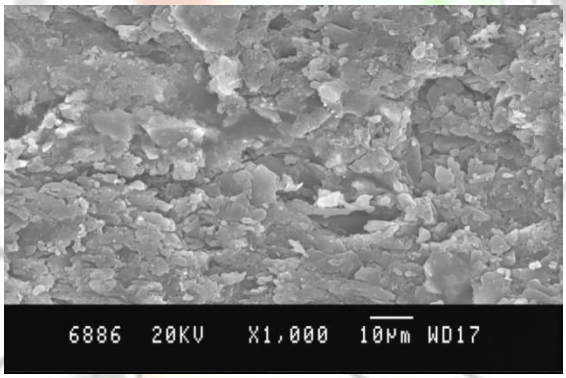


Fig. 1: Cumulative drug release study of different batches of floating tablets

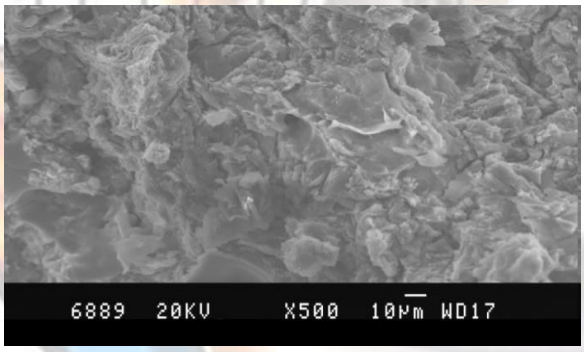
Figure 2: S.E.M. Images of dry tablet



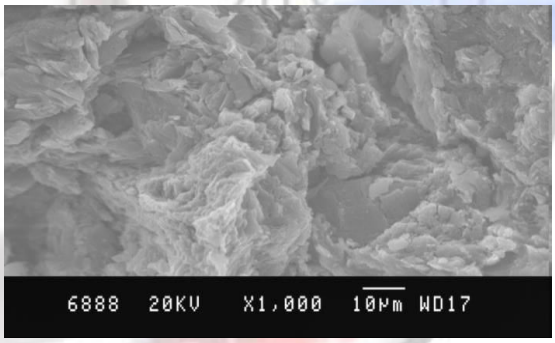
(1) Surface tablet.



(2) Surface table



(3) Fractured tablet (Cross portion)



(4) Fractured tablet (Cross portion)

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Fig. 3: Picture of Floating Tablet of Theophylline (Optimized Formula)

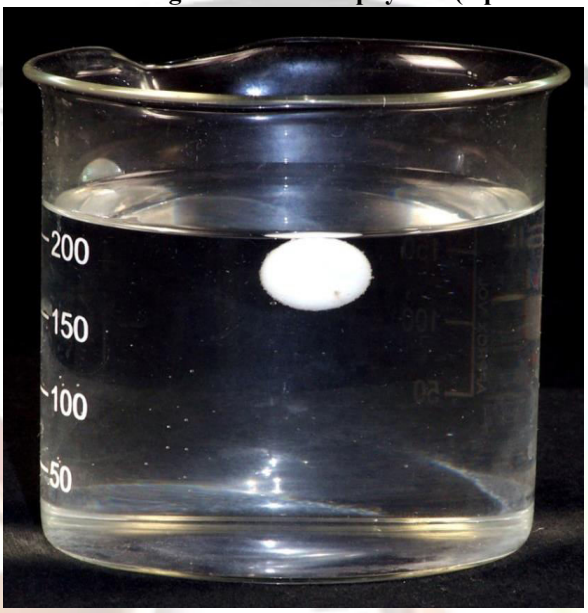


Fig. 4: D.S.C. image of theophylline

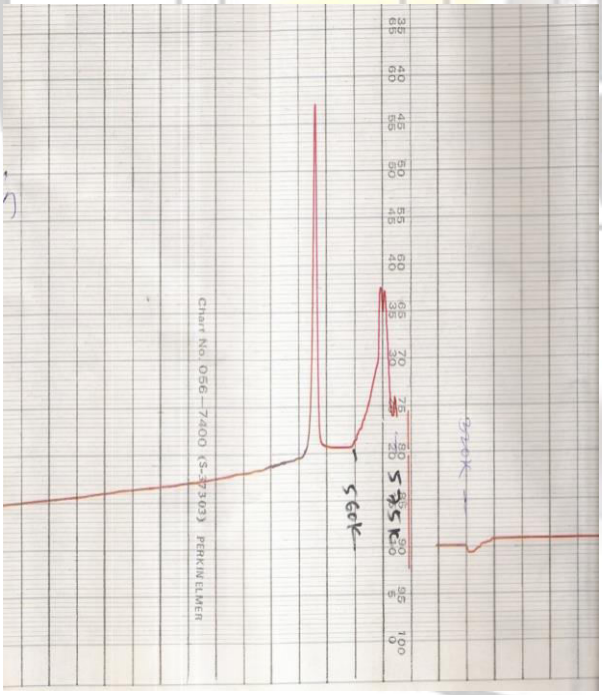
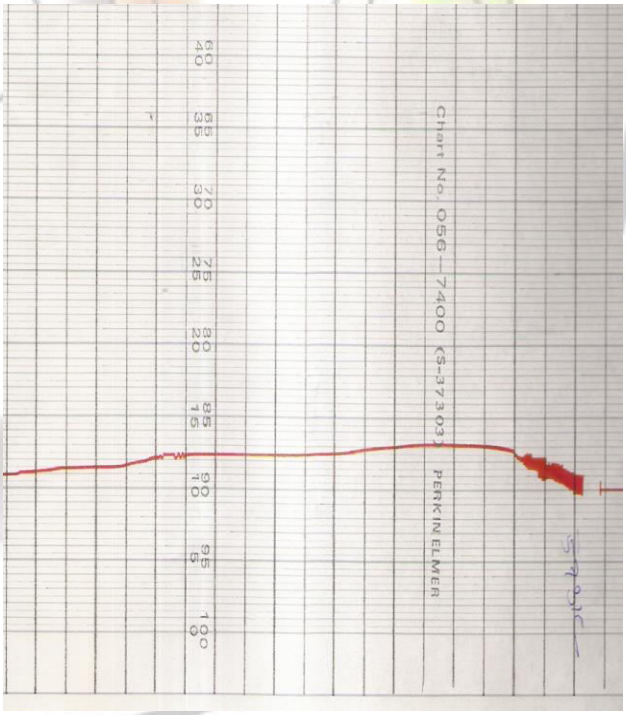


Fig. 5: D.S.C. image of HPMC (K100M)



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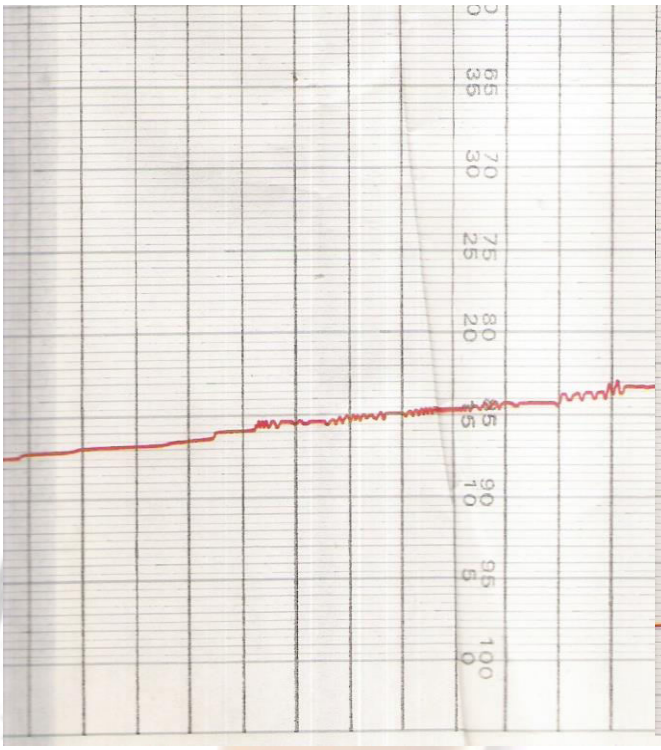

Fig. 6: D.S.C. image of theophylline and HPMC (k100M)

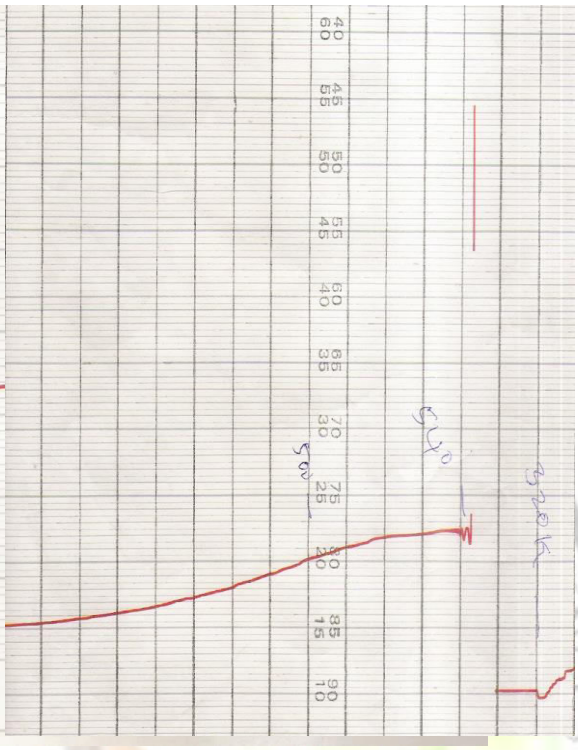

Fig. 7: D.S.C. image of Carbopol 934P

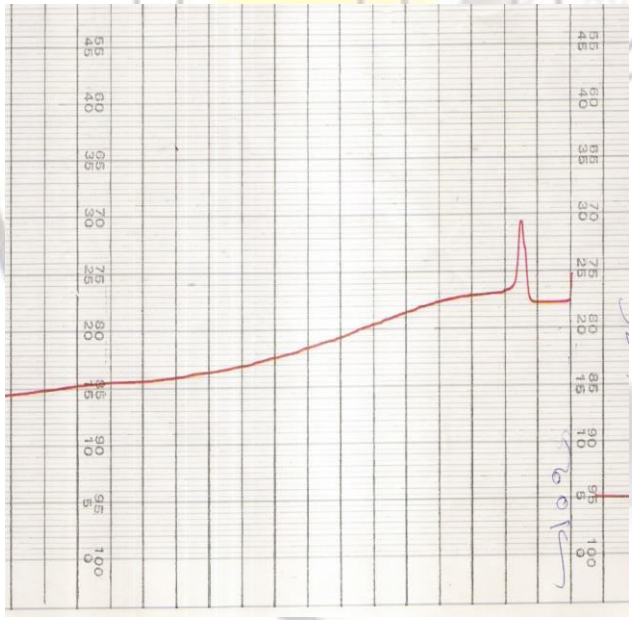

Fig. 8: D.S.C. image of theophylline and Carbopol 934P

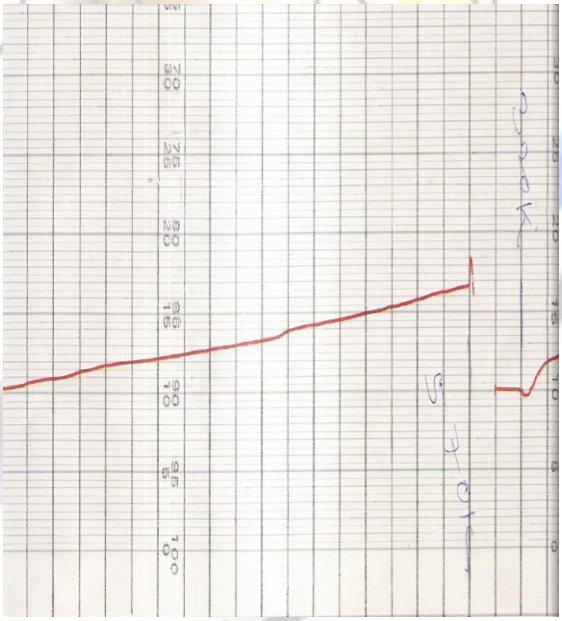

Fig. 9: D.S.C. image of dibasic calcium phosphate

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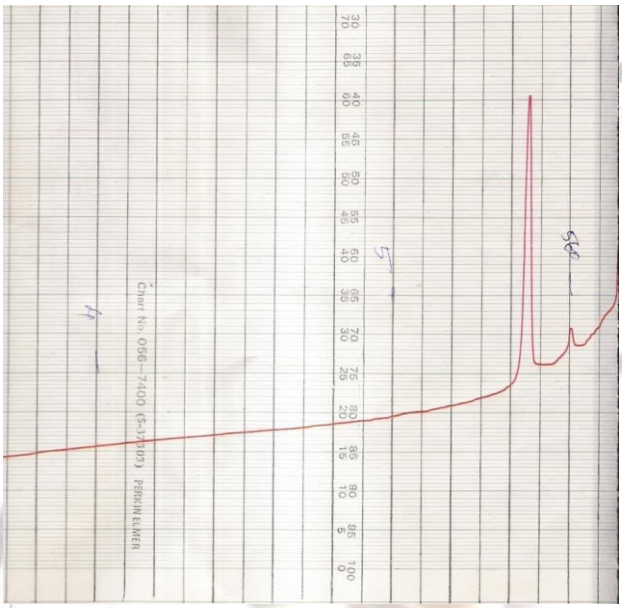

Fig. 10: D.S.C. image of theophylline and dibasic calcium phosphate

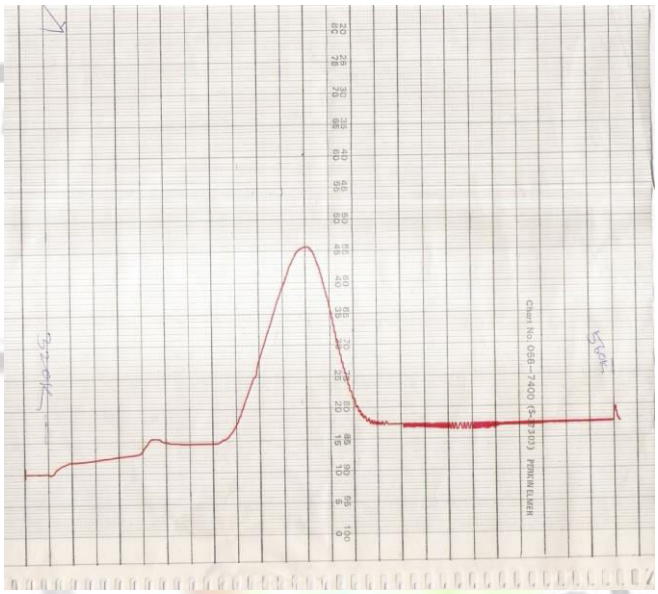

Fig. 11: D.S.C. image of Sodium bicarbonate

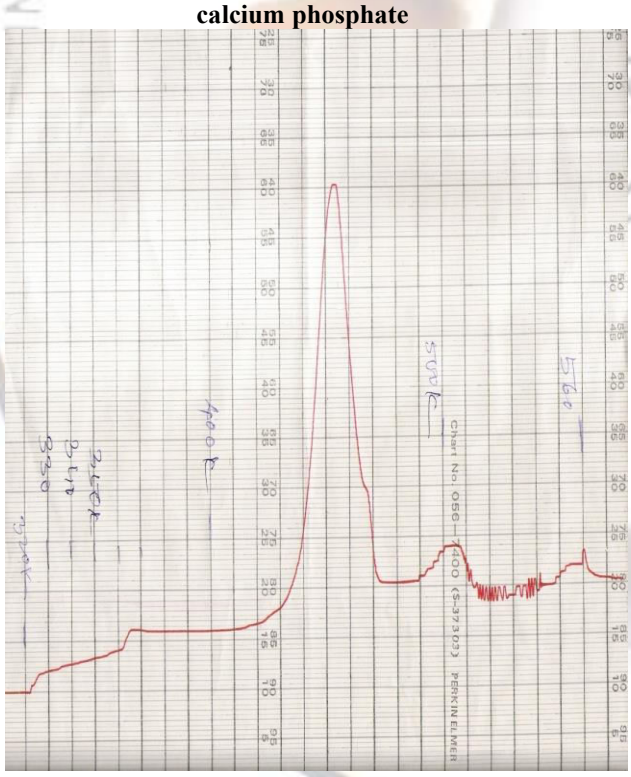

Fig. 12: D.S.C. image of theophylline and Sodium bicarbonate

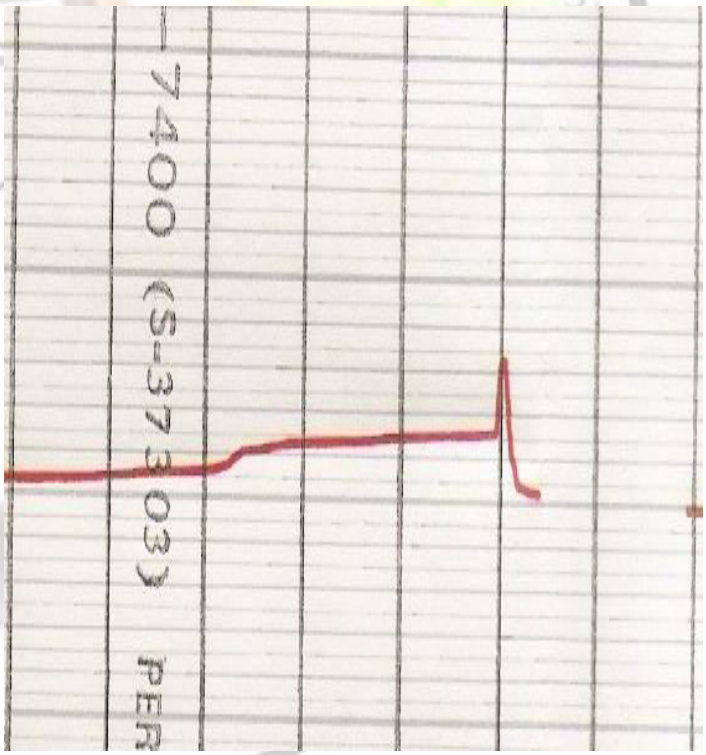

Fig. 13: D.S.C. image of PVP K30

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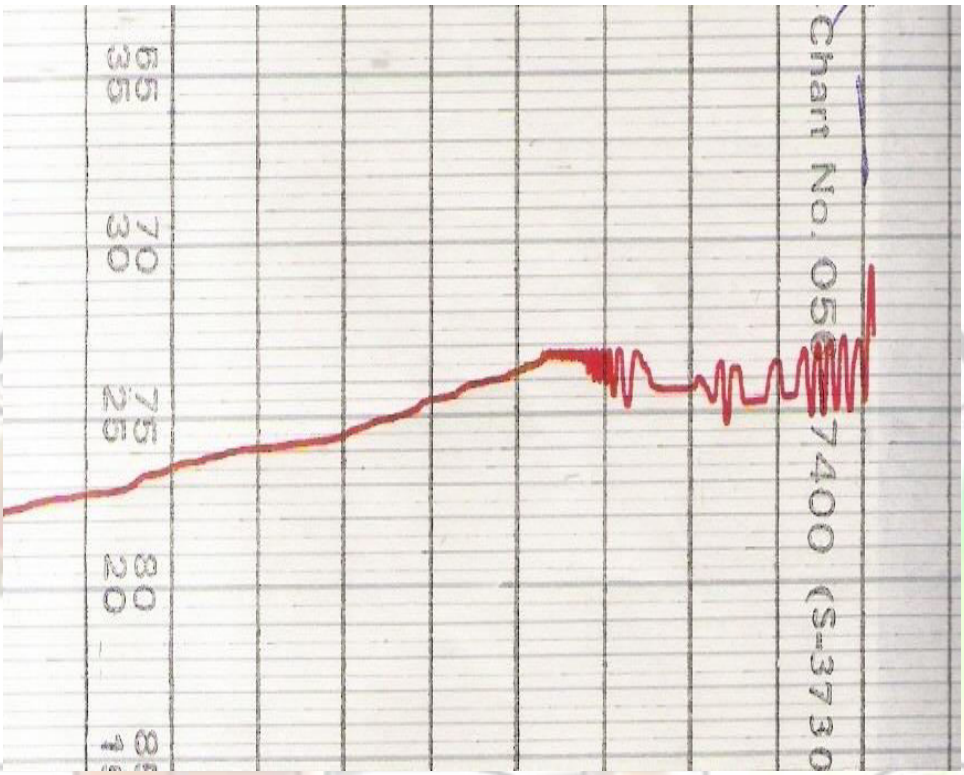

Fig. 14: D.S.C. image of theophylline and PVP K30