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Studies on Formulation and Evaluation of Ranitidine Floating Tablets

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Present investigation highlights the formulation and optimization of floating tablets of ranitidine hydrochloride. Formulations were optimized for type of filler, different viscosity grades of hydroxypropylmethylcellulose and its concentration. Two filler namely Avicel PH 102 and Tablettose 80 were used. Study revealed that type of filler had significant effect on release of drug from hydrophilic matrix tablets (*f* 2 value 41.30) and floating properties. Three different viscosity grades of hydroxypropylmethylcellulose namely K100 LV, K4M and K15M were used. It was observed that viscosity had a major influence on drug release from hydrophilic matrices as well as on floating properties. Dissolution profiles were subjected various kinetic drug release equations and found that drug release from hydrophilic matrices occurred via diffusion mechanism following square root of time profile (Higuchi equation). Optimized formulation were studied for effect of hardness on floating properties, effect of position of paddle and dissolution medium on drug release as well as accelerated short term stability study. Hardness of tablets had greater influence on floating lag time which might be due to decreased porosity. Position of paddle and types of dissolution medium had no significant effect on drug release. Optimized formulation was found to be stable at 40°/75% RH for the period of three months.

The *de novo* design of an oral controlled drug delivery system should be primarily aimed at achieving more predictable and increasing bioavailability of drugs[1]. The objectives of peroral controlled drug delivery system are to maintain therapeutically effective plasma drug concentration levels for a longer duration there by reducing the dosing frequency and to minimize fluctuations in the plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner[2]. Using controlled release technology, oral delivery for 24 h is possible for many drugs; however, the drug must be absorbed well throughout the whole gastrointestinal tract[3]. Oral sustained drug delivery system is complicated by limited gastric residence times which led to incomplete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine[4]. A significant obstacle may arise in development of oral controlled drug delivery if there is a narrow absorption window for drug absorption in gastrointestinal tract, if a stability problem exists in gastrointestinal fluid and if drug is poorly soluble in the stomach or degrade colonic microbial environment3. Thus the real issue in the development of oral controlled release dosage form is not just to prolong the delivery of the drugs for more than 12 h, but to prolong the presence of the dosage form in the stomach or somewhere in the upper small intestine until the drug is released for the desired period of time[5,6]. It was also suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage forms with prolonged gastric residence time would enable an extended absorption phase of the drugs[7]. It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug content is release, it would have limited utility.

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It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in 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 GI tract is to control gastric residence time i. e. gastro retentive drug delivery system, which will provide us with new and important therapeutic options[8] which utilize, several approaches: Intragastric floating system, high density system, mucoadhesive system, magnetic system, unfoldable, extendable or expandable and super porous biodegradable hydrogel systems. From the formulation and technology point of view, the floating drug delivery system is considerably easy and logical approach in development of gastroretentive drug delivery system[1].

Ranitidine is a drug of choice in the treatment of gastric ulcer and Zollinger Ellision syndrome and readily absorbed from gastrointestinal tract[9]. The bioavailability of ranitidine hydrochloride following oral administration is about 50% which might be due to colonic degradation by colonic bacteria[10]. Pithwala and co-worker[11] reported that the bioavailability of ranitidine hydrochloride is markedly lower from the human colon than the upper part of GI tract. The similar finding also reported by Basit and co-workers[12] that mean absolute bioavailability of ranitidine from the immediate release, small intestinal release and colonic release formulations were 50.6, 46.1 and 5.5 %, respectively. It was suggested that if the drug exhibits reduced or no absorption in the colon then a gastroretentive dosage form would be required to ensure drug delivery within drug absorbable intestinal regions[2].

Various attempts have been made to develop floating systems. Researcher used empty globular shell with a lower density than that of gastric fluid[13]. The other group of researchers developed a system comprising a drug and hydrocolloid mixture that swells and forms a soft mass floating on the top of gastric fluids[14]. Another possibility is to make gel-type matrix in which light oil and drugs are incorporated[15] or to produce a bilayer capsule comprising one layer is a release layer and other one is a floating layer[16]. The present study focused on development of a matrix floating tablet with an incorporated high dose of a freely soluble active substance.

MATERIALS AND METHODS

Ranitidine hydrochloride was used as a model drug obtained as a gift sample from Torrent Pharmaceuticals, Ahmedabad. Hydroxypropylmethylcellulose, HPMC K4M, K15M, K100LV were obtained as a gift sample from Colorcon Asia Pvt. Ltd., Goa. Microcrystalline cellulose, Avicel® pH 102 was obtained as a gift sample from FMC Biopolymer, USA. Spray dried lactose: Tablettose 80 was obtained as a gift sample from Meggle Gmbh, Germany.

TABLE 1: COMPOSITION OF FLOATING TABLETS OF RANITIDINE HYDROCHLORIDE

Ingredients (mg)	Batch Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	202	202	202	202	202	202	202	202	202
HPMC K4M	150	150	--	150	--	150	150	125	112.5
HPMC K15M	--	--	--	--	150	--	--	--	--
HPMC K100 LV	--	--	150	--	--	--	--	--	37.5
$NaHCO_3$	25	25	25	25	25	25	25	25	25
Avicel PH 102	118	88.5	118	59	--	29.5	--	143	118
Tablettose 80	--	29.5	--	59	118	88.5	118	--	--
Mg sterate	5	5	5	5	5	5	5	5	5
Total(mg)	500	500	500	500	500	500	500	500	500
FLT(sec)	40	60	60	90	90	120	150	60	60
TFT(h)	>12	>12	6.5	>12	>12	>12	>12	>12	>12

FLG is floating lag time and TFT is total floating time

Sodium bicarbonate, hydrochloric acid (36.2 %) and magnesium stearate were all of pharmaceutical grade and used as received.

Preparation of floating hydrophilic matrix tablet:

All the ingredients except magnesium stearate were homogeneously blended for sufficient time and then magnesium stearate was added and again mixing was done for 3 min. The homogeneously mixed blend of each batch was compressed using 12 mm standard concave punch (single punch tablet machine, Cadmach, Ahmedabad).The composition of all batches is given in Table 1.

Physical properties of floating tablets:

The prepared tablets were tested for weight variation, friability (Roche Friabilator, Electrolab, Mumbai) and crushing strength (Pfizer hardness tester). The average weight and standard deviation were calculated for weight variation test. (n = 20). The assay was carried out as per USP 24[17].

Floating properties:

The time the tablet took to emerge on the surface of dissolution medium (floating lag time) and the time the tablet constantly float on the surface of medium (total floating time) were evaluated in a dissolution vessel (dissolution apparatus Veego scientific, Mumbai) filled with 900 ml of 0.1 N HCl (pH 1.2) previously set at 37 ± 0.5^0 with paddle rotation at 100 rpm[3].

***In vitro* drug release:**

The drug release studies were carried out using USP 24 type II dissolution apparatus. The dissolution vessels were filled with 900 ml of the 0.1 N HCl using paddle rotation of 100 rpm and temperature was kept constant at 37 ± 0.5^0. The samples were withdrawn at predetermine time intervals and each time fresh medium was replaced in same amount. The samples were suitably diluted and the absorbance was measured spectrophotometrically (UV/Vis, Shimadzu UVPC 2401, Singapore) at wavelength of 313 nm against 0.1 N HCl as a blank. The content of drug in each sample was calculated using a standard calibration curve. The *in vitro* drug release was carried out in triplicate for each batch of tablets. To study the effect of hardness on floating lag time, the tablets of batch F2 were compressed to obtain a hardness of 4 kg, 7 kg and 10 kg and the floating lag time was determined.

Mechanism of drug release:

To find out the mechanism of drug release from hydrophilic matrices, the dissolution data of tablets of each batch treated with different kinetic release equations[18]. Namely zero order: $Q = K_0t$; Higuchi's square root at time: $Q=K_H\ t^{1/2}$ and Korsmeyer and Peppas: $F=K_m\ t^n$, where Q is amount of drug release at time t, F is fraction of drug release at time t, K_0 is zero order kinetic drug release constant, K_H is Higuchi's square root of time kinetic drug release constant, K_m is constant incorporating geometric and structural characteristic of the tablets and n is the diffusion exponent indicative of the release mechanism. The value of n for a cylinder is <0.45 for fickian release, 0.45 to 0.89 for non Fickian release, 0.89 for the case II transport and >0.89 for the super case II type release.

Effect of position of paddle on drug release:

The position of paddle was set at surface of dissolution medium as the floating tablet was remained constant on surface of dissolution medium. To carry out the dissolution the position of paddle was changed and similar methodology adopted as described *in vitro* drug release study. The dissolution was carried out for tablets of batch F2.

Effect of dissolution medium on drug release:

The effect of various dissolution medium on drug release was studied as the dosage form passes through the various segments of GI tract. For the study, the dissolution was carried out using distilled water and phosphate buffer as a dissolution medium. In case of phosphate buffer (pH 6.8), the first 4 h dissolution study was carried out in 0.1 N HCl and thereafter the dissolution was continued in phosphate buffer pH 6.8 as a dissolution medium. The dissolution study was carried out same as described *in vitro* drug release study on tablets of batch F2.

Comparative evaluation of dissolution profiles:

To evaluate and comparing the dissolution profile of tablets of each batch whenever necessary, was made using similarity factor $f2$ which may be defined as follows[19]. $f2=50\ \log\ \{[1+1/n\ x\ w_t(R_t-T_t)^2]^{-0.5}x100\}$, Where n is the number of pull points, wt is an optional weight factor, Rt is the reference assay at time point t and Tt is the test assay at time point t. The $f2$ value between 50 and 100 suggests that the dissolution profile is similar. The $f2$ value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between release profiles increases.

Characterization and stability study of tablets:

Tablets of batch F2 were put on short term stability study at 40°/75%RH condition for the period of three months. The tablets were evaluated for *in vitro* drug release after each months and dissolution profile evaluated using similarity factor $f2$. Tablets of batch F2 was characterized using differential scanning calorimetry (DSC) for any physical as well as chemical incompatibility between drug and polymers.

RESULTS AND DISCUSSION

The average weight of tablets of all batches found in range of 0.497 to 0.500 g with standard deviation in range of 0.0005 to 0.0020. The % friability ranges from 0.62 to 0.80% and the hardness was 4-5 kg. The assay of tablets of all batch found in range of 98.5 to 99 %. From the results, it was observed that the tablets of all batches had acceptable physical characteristics.

From the study of floating properties (Table 1), it was observed that the floating lag time ranges from 15 to 180 s and tablets of each batch except batch F3 had total floating time of more than 12 h. In later case it was observed that the tablet dissolved in 6.5 h only which might be due to low viscosity of polymer (100 cps). This finding was in good agreement by study of Li and co-workers[20] who reported that HPMC of higher viscosity grade generally exhibited greater floating capability. The higher floating lag time was observed in tablets of batch F4, F6 and F7 which might be due to presence of higher amount of lactose than the tablets of batch F2 as it is well known to the ordinary in the art of excipient that the lactose has higher density than microcrystalline cellulose.

From the dissolution profiles of all batches (fig. 1), it was observed that tablets of batch F5 gave comparatively good dissolution profile despite of presence of high viscosity grade of HPMC (15000 cps) which should decrease the drug release compared to tablets of batch F7 containing the same amount of HPMC K4M (4000 cps). The good dissolution profile may be due to high amount of water soluble filler lactose in the hydrophilic matrix that might create the path for drug release and weaken the matrixing ability of HPMC K15M. The high amount of lactose in matrix along with high soluble drug may lead to brushing effect in case of tablet of batch F5 and batch F7 having 25.9 and 31.6 % drug release in 1 h. Tablets of batch F1 and F3 also not gave satisfactory dissolution profile as the former had slower release of about 65.51 after 8 h which might be due to high amount of water insoluble filler, microcrystalline cellulose. The tablets of batch F3 was dissolved in 6.5 h which might be due to low viscosity of polymer.

Tablets of batch F2, F4 and F6 gave somewhat similar dissolution profile. As discussed earlier the tablets of batch F4 and F6 had higher floating lag time and also gave 24.9 and 26.2 % drug release in 1 h compare to 24.7 % drug release in 1 h of tablets of batch F2. From the ongoing discussion, it was concluded that tablets of batch F2 had good performance among the batch F1 to batch F7.

To investigate the effect of small variation in concentration of HPMC on drug release, batch F8 was prepared in which the concentration of HPMC K4M reduced to 25 % w/w of tablet and rest of composition was same as

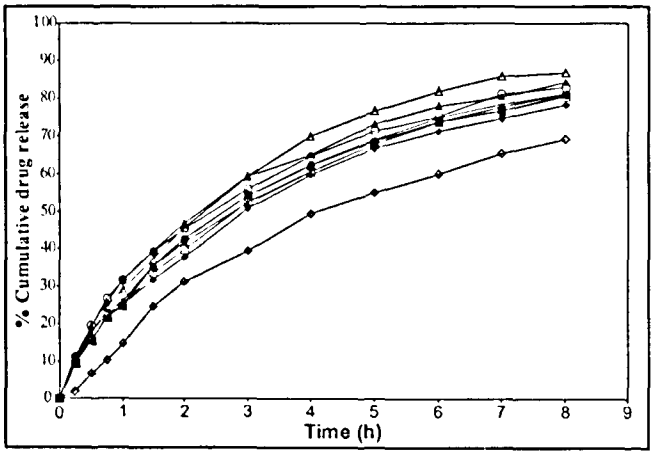

Fig. 1: Dissolution profile of ranitidine floating tablet in 0.1 N HCl

F1 (-◇-), F2 (-□-), F3 (-Δ-), F4 (-O-), F5 (-*-), F6 (-■-), F7 (-o-), F8 (-▲-), F9 (-♦-)

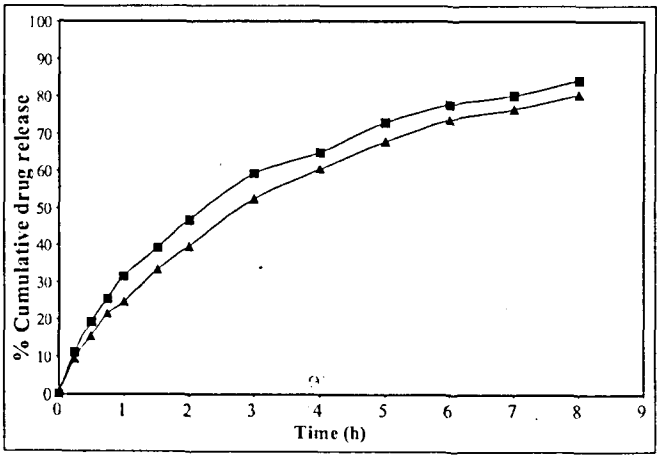

Fig. 2: Effect of content of polymer on drug release (-▲-) 30 % w/w HPMC K4M, (-■-) 25 % w/w HPMC K4M

TABLE 2: KINETIC TREATMENT TO DISSOLUTION PROFILE OF TABLETS

Batch	Zero order			Higuchi			Korsmeyer and Peppas		
	n	r^2	K	n	r^2	K	n	r^2	K
F1	8.68	0.973	7.94	30.20	0.997	13.67	0.959	0.976	0.401
F2	9.16	0.969	16.60	31.95	0.997	5.83	0.623	0.995	0.542
F3	10.04	0.959	19.30	35.31	0.992	5.72	0.635	0.991	0.566
F4	9.12	0.963	17.55	31.98	0.994	5.05	0.623	0.993	0.547
F5	8.99	0.971	17.98	31.34	0.997	3.99	0.588	0.996	0.557
F6	9.02	0.967	18.75	31.55	0.996	3.46	0.585	0.995	0.562
F7	8.88	0.962	21.55	31.18	0.994	0.528	0.557	0.991	0.583
F8	9.07	0.957	21.67	31.96	0.992	1.045	0.568	0.991	0.584
F9	8.82	0.972	16.62	30.72	0.996	4.877	0.594	0.997	0.545

that of batch F2. From the dissolution profile of tablet of batch F8, it was observed that decreasing the concentration of HPMC, the release rate of drug was increased (fig. 2) but found insignificant as the value of similarity factor $f2$ was found to be 64.46. The results were in good agreement by study of Sunada and Xu[21] who reported that HPMC contents was the predominant controlling factor, as the HPMC content increased, the drug release rate decreased and *vice versa*.

To investigate the effect of small variation in viscosity of polymer on drug release, tablets of batch F9 were prepared by replacing 25 % W/W of HPMC K4M with HPMC K100 LV and rest of component same as tablets of batch F2. From the results it was observed negligible effect on overall drug release profile compared to batch F2 (fig. 3) as value of $f2$ found to be 86.44. The burst effect observed in tablets of batch F9 as 25.1 % drug release in 1 h compare to 24.7 % drug release in 1 h of tablets of batch F2 which might be a period of burst effect afterwards the no significant difference was observed. The results were also supported by Li and co-workers[22], who reported there is a significant difference in burst effect from formulations fabricated from polymers with different viscosity grade but not significant difference observed for second phase of drug release which might suggest that the initial burst effect is followed by the

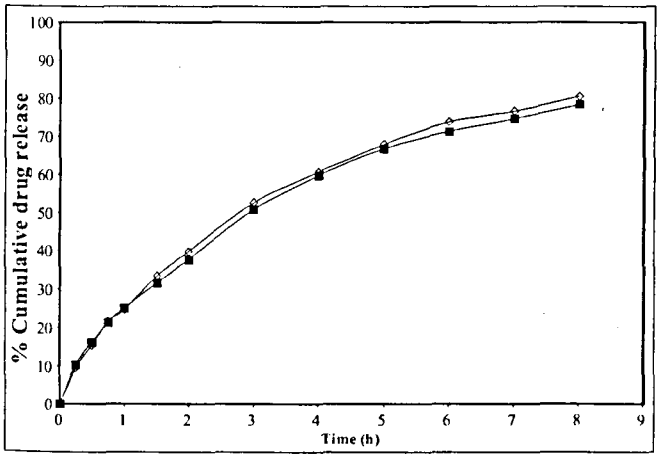

Fig. 3: Effect of small variation of viscosity of polymer on drug release

(-◇-) HPMC K4M, (-■-) HPMC K4M: HPMC K100LV (75:25)

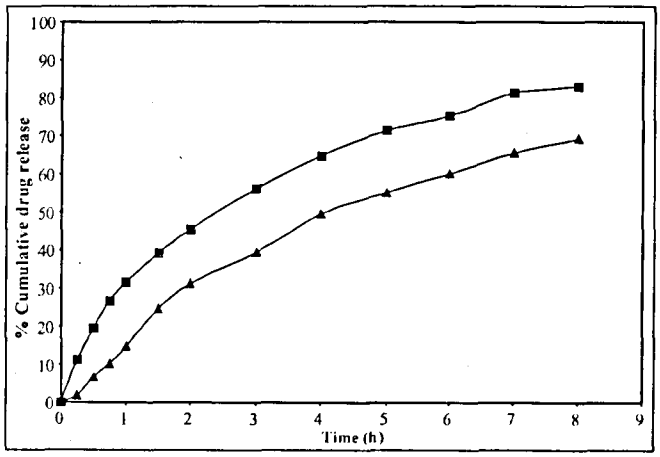

Fig. 4: Effect of type of filler on drug release

(-▲-) MCC, (-■-) Lactose

completion of a stable gel layer which in turn controls the drug release from drug delivery system.

It was observed that there was significant influence of type of filler on drug release (fig. 4) as the change of water insoluble filler, microcrystalline cellulose (Batch F1) to water soluble filler, lactose (Batch F7), the release was significantly higher in later case as observed in dissolution profile of batch F7 compared to batch F1 and found significant as $f2$ value was 41.3, which might be due to higher solubility of lactose which weaken the matrixing ability of HPMC K4M and created path for drug to be released as well as reduction of tightness of swollen hydrogel[23].

From the results of dissolution data fitted to various drug release kinetic equations (Table 2), it was observed that highest correlation found for Higuchi's square root of time profile which indicates the drug release occurred via diffusion mechanism from hydrophilic matrices of HPMC. The results were in good agreement by studies of Hashim and co-workers[24] and Ford *et al.*[25]. Hashim and co-workers[24] reported that potassium chloride compressed with HPMC followed a square root of time profile in a range of 15 to 95% of drug release. Ford *et al.*[25] reported that the soluble drugs, promethazine hydrochloride, aminophylline and propranolol hydrochloride were released by square root of time (Higuchi) kinetic from HPMC matrices in a range of 5 to 70% drug release and is appeared that for soluble drug, therefore square root of time plots presents good approximation of release kinetics.

Buoyancy of tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids, which in turns in an increase in the bulk volume and the presence of internal void in the dry centre of the tablet, porosity[26]. On increasing the hardness of tablets of batch F2 from 4 kg, 7 kg and 10 kg resulted in significant increase in floating lag time from 60 sec, 160 sec, and 900 sec, respectively which might be due to higher compression may results in reduction of porosity of the tablets (fig. 5) and moreover, the compacted surface hydrocolloid particles on the surface of the tablets cannot hydrate rapidly when the tablet contacts the gastric fluids and as a results of this the capability of the tablet to float is significantly reduced[26].

From the results of dissolution profile of tablets of batch F2 when position of paddle set of surface of dissolution medium, it was observed (fig. 6) that there was not significant change in dissolution profile of tablet compared to dissolution profile of tablets when paddle position set as per standard specification as the value similarly factor $f2$ was found 64.76 although the drug release was found faster (burst effect) in 1 h which might be due to intense agitation force of paddle when it set at surface of dissolution medium as floating tablet remains on surface of dissolution medium but as the tight gel layer formed there was not significant difference in dissolution profile of tablet. From the results of dissolution profile of tablets of batch F2 when using distilled water and phosphate buffer pH 6.8 (after 4 h dissolution in 0.1 N HCl) as a dissolution medium, it was observed that (fig. 7) release rate was somewhat higher when using distilled water and phosphate buffer which might be due to better solubility of drug in water and phosphate buffer compare to 0.1 N HCl. But the difference was not significant

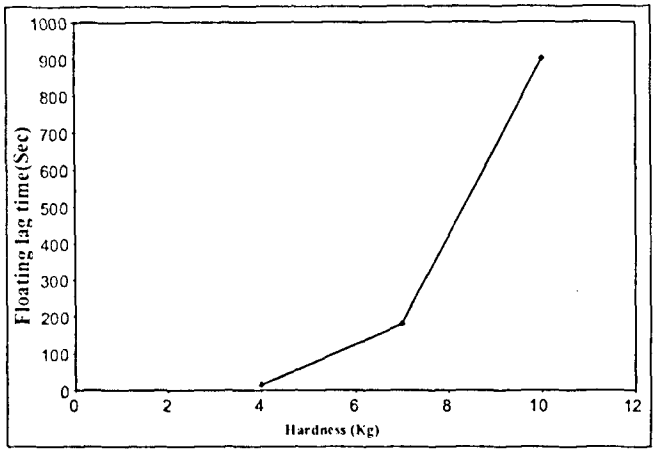

Fig. 5: Effect of hardness on floating lag time of tablet of batch F2

(-◆-) floating lag time

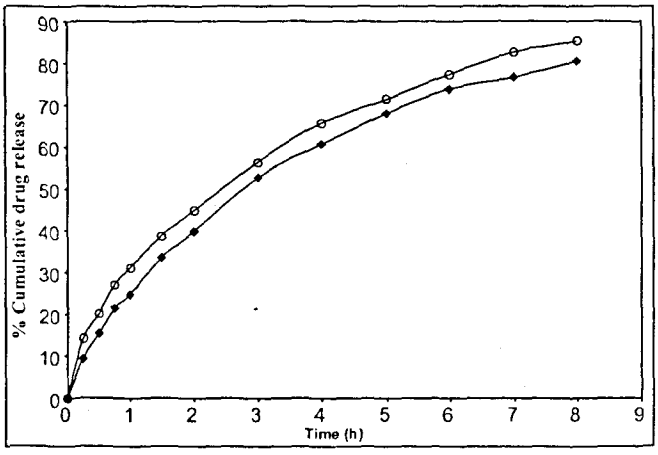

Fig. 6: Effect of position of paddle on drug release of tablet of batch F2

(-◆-) Normal position, (-o-) Modified position

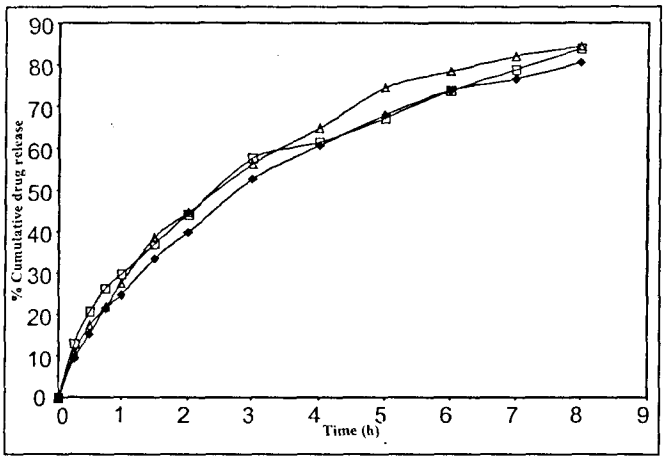

Fig. 7: Effect of dissolution medium on drug release of tablet of batch F2

(-◆-) 0.1 N HCl, (-□-) Distilled water, (-△-) 0-4 h in 0.1 N HCl & 4-8 h in Phosphate buffer

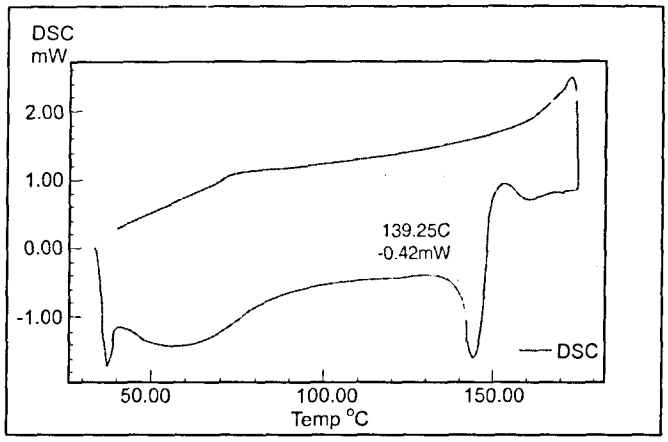

Fig. 8: DSC thermogram of tablet sample

as the *f*2 value was found 70.9 and 68.79 for distilled water and phosphate buffer with reference to 0.1 N HCl, respectively.

Tablet of batch F2 was characterized by DSC for any pnysical and chemical incompatibility and it was observed that (fig. 8) there was not any significant change in melting point peak of drug in tablet sample which indicate there was no physical as well as chemical incompatibility of drug with the formulation excipients.

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