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Influence Of Sample Preparation Method On Isothermal Studies During Compatibility Screening Of Ofloxacin; Correlation With DSC Data

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Abstarct

Objectives: The compatibility of ofloxacin with some commonly used diluents has been investigated using isothermal stability studies (IST) to allow relative ranking.

Materials and Methods: The samples were prepared using three methods namely physical admixtures (with 5% added moisture), slugging and kneading in order to evaluate the effect of mechanical treatment on the physicochemical stability of drug. To further verify the results of IST fresh binary mixtures were subjected to thermal analysis and an attempt was made to correlate the results obtained from the two studies.

Results: The results from both DSC and IST revealed that ofloxacin was compatible with all the diluents used in the study. Among the three methods of sample preparation used for the study, the extent of degradation was more or less same in all the three methods indicating least influence of method of sample preparation on the results of IST.

Conclusions: From the study it was concluded that a better co-correlation could have been obtained had ofloxacin been more unstable with few of the excipients than rest, used in the study. This way the extent of degradation would be distinguishing enough to rank the excipients in decreasing order of stability.

Key words:

Compatibility, Diluents, DSC, Isothermal Stability Studies, Ofloxacin.

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Introduction

The identification of possible incompatibilities between drug and excipients is one of the basic tasks to be dealt within a preformulation laboratory [1]. Generally excipients are major fraction of solid dosage form and provide protection of drug from direct exposure to external environment [2, 3].

For rational drug development it is essential to characterize the physicochemical properties, polymorphic forms and stability of the new chemical entity, as well as to assess its compatibility with excipients during processing and storage to obtain final drug product [4]. Over the years compatibility study is being done by using sophisticated instrumental methods for selection of excipients, however it is not always successful and this has led some authors to question its utility [5-7].

In order to develop a successful compatibility method an experimental design that furnishes the required information with minimum experimental efforts is often required. To achieve this objective it is essential to have a correct choice of experimental method in the light of both the accuracy required and of the various pitfalls, which are likely to be encountered, including the number, spacing and interrelation of the individual observations.

For routine drug- excipients interaction study in a quantitative manner, normally isothermal stress results are coupled with results of DSC are considered sufficient. However there are very few reports wherein thermal interactions are confirmed with routine stability testing, involving chemical analysis [8-17].

In the present study compatibility of ofloxacin was assessed with some commonly used excipients. Ofloxacin is one amongst the new generation of fluorinated quinolones structurally related to nalidixic acid with broad spectrum antibacterial activity [18].

For compatibility screening, 3 different methods were used to prepare drug excipient binary mixtures, namely physical admixing with 5% moisture, kneading and slugging. All the binary mixtures were prepared in 1:1 ratio to increase the likelihood of observing any

interaction [19]. The results of stability studies and the changes in thermal parameters of drug, excipients and binary system of drug and excipients obtained from DSC were then correlated.

Materials and Methods

Material

Ofloxacin (OF) was obtained as gift sample from Cipla Ltd., Mumbai, India. Microcrystalline cellulose pH101 and pH102 (MCC) (Chemsfield, Nagpur, India), Emcompress (JRS, USA.) Neosorb, Lycatab and Pearlitol (Roquette Inc. USA.), Lactochem Fine powder and Lactopress spray dried (Borculo Domo ingredients, The Netherlands), Dicalcium phosphate anhydrous (Merck Ltd., Mumbai, India) and Dextrose anhydrous (Cipla Ltd, Mumbai, India) were received as generous gift samples. All other chemicals and reagents used were of A.R. grade. Water used in all the experiments was double distilled.

Experimental Method

Preparation of solid binary system for isothermal stability studies

Each material was sieved through # 100 mesh (approx 150μm). Physical admixtures (P.Ad.) of ofloxacin and each selected excipient with 5 % added water were prepared in 1:1 w/w ratio by gently blending in mortar pestle. Kneaded mixtures were prepared by slurring a portion of binary mixture with minimum amount of ethanol and triturating thoroughly to obtain paste, which was dried under vacuum at 50°C up to a constant weight (Micro Instruments, Delhi, India) and used for further studies. Slugged mixtures were prepared by subjecting binary mixtures to flat face punches on tabletting machine (Cadmach Ltd., Ahmedabad, India); triturating the slugs to obtain (#100) 150μm granulometric fraction, and using this further for IST studies. The binary mixtures were divided into two equal parts for storage and analysis. A control sample of pure drug and reference samples of pure drug with moisture, pure drug with solvent, and pure drug slugged, were also prepared in similar manner and subjected to analogous conditions.

Storage and analysis of samples

Binary mixtures prepared by all methods were stored at 2 condition 30 ± 2°C, and 50± 2°C. All the admixtures were stored in amber colored bottles (2 bottles for each binary mixtures) with tight fitting screw caps and sealed with adhesive tape. In each case, one bottle was kept at ambient conditions ~RT (30±2°C), while the other was stored in oven (Spectrum, India) with temperature adjusted at 50±2°C. Duplicate samples were withdrawn from each bottle at different time points and analyzed spectrophotometrically. The sampling points for samples stored at 30 ± 2°C was 0, 15, 30, 45, 60, 90,135, and 180 days while for samples stored at elevated temperature (50 ± 2°C) was 0, 8,15, 22, 30, 45, 60, 90,135, and 180 days respectively. The blends were also examined for any unusual color change.

The preparation of sample for analysis involved weighing of 20 mg admix (10 mg in case of pure drug), diluting the same with 100mM HCl to obtain 10 mcg/ml concentrations and analyzing against blank, at 293 nm [20]. Drug content was determined from the calibration curve prepared within the same range of 2-25 mcg/ml. The method was found to be linear with studied range (R^2=0.999). The percent drug remaining values were calculated, taking the assay values at the end of six-month study, of pure drug reference as 100% (considering the fact that pure drug reference will exhibit the effect of sample preparation method and will mimic the stress exhibited by binary mixtures in more better manner thereby acting as a benchmark for comparison rather than pure drug control sample without added moisture/ slugging process/ added solvent) and then calculating the amount of drug remaining in all other binary mixture with respect to reference.

Data acquisition was carried out on UV-visible spectrophotometer (UV-Pharmaspec) from Shimadzu, Japan, provided with UV probe 2.01version software.

Stability studies in liquid state

For stability of drug in liquid state an excess of excipients (1g) was added to 100 ml of solution of ofloxacin having strength of 10mcg/ml in100mM HCl (pH 1.4). Series of such solutions with other excipients were also prepared in iodine flask and kept in water bath shaker (Remi Equipments, Nagpur, India) at speed of 50 RPM for 72hrs. The temperature of the water bath was maintained at 37±2°C. Aliquots from these flasks were withdrawn initially and after 72 hrs (triplicate), filtered (Whatman filter paper no-2) scanned and analyzed for changes in absorbance (λ_{max} 293 nm) and changes in pH (μ pH system, Systronics, India). Solution of pure drug was also prepared (control) and subjected to analogous condition.

Differential Scanning Calorimetry

All measurements were carried out on an indium calibrated DSC Q10 V9.4 build 287 (TA instruments, USA) provided with refrigerated cooling system. Data was analyzed using the universal analysis 2000 software (TA instruments, USA). Individual samples (drug and excipients #100 mesh) as well as freshly prepared admixtures of drug and selected excipients (2-4 mg) were weighed directly on DSC aluminum pan and scanned between 30-350°C at a heating rate of 20°C/min in an atmosphere of dry nitrogen (50ml/min flow rate). Sample pans were not crimped; instead lids were gently placed on the pan and covered, to allow for exchange of gases if any, so as to prevent bursting of pan. An empty pan with lid kept in similar manner was used as reference. Mettler AB-264 balance (Mettler, Switzerland) was used for weighing of samples.

Results and Discussion

Isothermal stability studies

Most often it is found that compatibility tests address only a limited number of variables and processing effects are usually ignored, which can significantly alter the solid-state properties of drugs and excipients. Hence, samples for IST studies were prepared keeping in view, the conditions likely to be encountered during formulation process. The results of IST studies along with the ranking of excipients on the basis of % drug remaining and first order degradation rate constants at

RT and 50°C is given in Table 1 and Table 2. The data in Table 1& 2 indicates that irrespective of the method of sample preparation in majority of drug diluent case, increase in temperature brought about marginal increase in the rate of decomposition. The increase was marginal hence clearly defined ranking of diluents for elevated temperature stability studies could not possible. With respect to role of temperature on ofloxacin degradation, RT decomposition was found to vary from a minimum of 1.5 - 2.6% for the samples prepared by all the three methods while at 50°C this variation quantum wise remained same lying in the region 1.5- 2.6 %. It was observed that moisture seems to play a catalytic role in particle-particle interaction than that by improved or relatively closer particle contacts induced by slugging or kneading method.

Hence, the conventional method of preparation of samples by simple trituration with 5% moisture could not be discounted in favor of slugging and kneading. It has been demonstrated earlier that addition of moisture in blends during compatibility screening facilitates the dissolution of drug and excipients in added water, resulting in disorderness and water absorbed in such phases accelerates drug decomposition [21]. In the present case catalytic effect of moisture appears to have become somewhat more noticeable at elevated temperature storage condition of 50°C. This in all probabilities seems to have resulted from increased drug dissolution, thereby making more amount of drug available in the form (molecular) in which it is more susceptible to decomposition. It may therefore be observed that effect of diluent on the stability of ofloxacin was hardly influenced by the method employed in sample preparation for preformulation stability studies.

The level of drug degradation at the end of 6 months in any of the binary mixtures was not significant hence it can be classify as compatible system. In case of incompatible system it was expected that the extent of decomposition would be magnified but this was not evident in binary system series prepared by all 3 methods since maximum decomposition at 50° was more or less same as that at 30°, using all the three methods of sample preparation. This was probably because of similar level of compatibility of ofloxacin with all the investigational diluents because of which no particular trend was observed in ranking of diluents at all the temperature.

Stability studies in liquid state

Various researchers have reported catalytic effect of magnesium stearate on aspirin decomposition based on hydrolysis taking place in an adsorbed layer and the alteration in the pH of this layer by added excipient [22]. It is often observed that change in pH affects the stability of drug and subsequently the impurity levels because some degradation reactions initiate/ accelerate at particular pH .

It is known that all quinolones are zwitterionic in character, due to presence of both a carboxylic acid and a basic amine, which induces a negative charge at higher pH and a net positive charge at lower pH. Because of this, quinolones tend to be more soluble in water at acidic and basic pH, with minimum solubility expressed at neutral pH values [23].

In the binary solution of ofloxacin with various excipients, the pH ranged from 1.42 to 1.80, except in case of emcompress and DCP-anhyd. Emcompress and DCP- anhyd., being alkaline excipients, pH of the binary solution of drug with these excipients showed maximum changes (3.02 and 2.88 respectively). However no significant absorption, adsorption, resulting in decreased drug content, was observed in any of the binary solutions. On comparing the positions of these two excipients in the Table1 and 2 for ranking of excipients, using all the 3 methods in IST studies, it is observed that DCP-anhyd., and emcompress are usually placed at the end of the ranking except in samples prepared by kneading method. The change in pH of solution of drug in presence of these excipients may be one of the contributing factors, for the ranking of these excipients. Patel [24] in their work on stability of aspirin reported higher pH-values of aspirin DCP-anhyd., mixtures compared to aspirin alone (at pH 2.5 aspirin has maximum stability) and concluded the possible role of pH in causing instability in the mixture. The change observed in pH values and drug content after 72 hrs. of study are listed in Table 3.

Differential Scanning Calorimetry

The samples for DSC analysis were simple binary mixtures prepared freshly, and no moisture / solvent was added in them.

In the DSC thermogram of ofloxacin, a single melting endotherm at 277°C was observed as reported in literature [20]. The DSC thermogram of MCC101, MCC102 (Fig. 1) and Lycatab showed an initial broad endotherm below 100°C, due to loss of adsorbed water on heating. In the thermogram of binary mixture of ofloxacin with MCC101 MCC102 and Lycatab (Fig.1), the characteristic endothermic features of both drug and excipients were retained. Van Dooren [25] had proposed that if the DSC thermogram of a binary mixture is a simple superimposition of the individual traces, an incompatibility is highly unlikely. On having a look at multiple ranking of diluents summarized in Table 1 and 2 not much difference could be observed between the compatibility ranking of MCC101, MCC102, and Lycatab with rest of the diluents under investigations. While MCC101, and MCC102 on the ten point's empirical scale, ranked from 1 to 8, and position 1 to 6 respectively, Lycatab was ranked in the range of 1-8. However, in all these three cases, the total enthalpy of the admixture comprising of drug and each of these diluents were undoubtedly preserved well above the theoretical minimum anticipated while considering enthalpy as an additive property in manner treated by Shattawy et al. [26]. It therefore follows that, if an excipient exhibits considerable thermal feature (perhaps an endotherm) just before the temperature at which drug melts, enthalpy loss suffered by drug at an endothermic event of such excipient is likely to be compensated by comparable improvement in the heat content of the excipient.

DCP-anhyd displayed no transitions in baseline in the scanned region (Fig. 2). Inspite of lack of any thermal event being associated with this diluent, ofloxacin experienced an enthalpy gain of as much as 37% (Table 5). According to the estimate of Shattawy and coworkers [26], if enthalpy loss is an index of incompatibility, enthalpy gain by the drug atleast, if not the entire system,

might be presumed to be a measure of not only absence of any incompatibility but drug stabilization also.

Emcompress like its structurally related analog DCP- anhyd preserved fusion endotherm of the drug very much at its characteristic melting point having the peak location at the temperature of 277.32°C (Fig.2). However, unlike DCP- anhyd that brought about gain in enthalpy of ofloxacin by about 35-40 % (Table 5), emcompress produced gain in enthalpy of the drug by 4%. Despite the fact that both these diluent are structurally related materials, drug enthalpy loss in one and gain in other, may in all probabilities be ascribed to their differences in thermal behaviors. Enthalpy loss of the drug in presence of emcompress seems to have been resulted from the presence, in emcompress, of conspicuous endothermal peak, at the temperature well below the melting point of the drug (Fig 2). Substantial increase in the heat content of this peak in presence of ofloxacin presumably indicates that occurrence of this endothermal event provides an environment conducive to initiate interaction between the drug ofloxacin and emcompress. As a result, summation of enthalpies of a lone endothermal feature associated with the drug as well as emcompress was very much close (Table 5), to the value expected from the proportionate participation of each component to the heat content exclusively of these two peaks, being contributed one each by the drug and the diluent emcompress. The multiple compatibility ranking of this diluent (Table1 and 2) which reveals broad variation from 4 to 10, does not appear to indicate any long term threat to the existence of ofloxacin in contact with emcompress. This presumably suggests that in presence of any excipient exhibiting prominent endothermal event in the vicinity (perhaps within 100°C) of melting temperature of the drug, measurement of enthalpy change (i.e. loss) of the drug alone is not sufficiently enough and the heat content of the complete system comprising of the drug and the excipient should be accounted for prior to compatibility incompatibility predictions involving thermal analytical techniques are ultimately made.

The DSC thermogram of Pearlitol and Neosorb (Fig. 3) revealed endothermic peaks corresponding to melting, with no decomposition in scanned range. In the scan of dextrose anhyd., an initial dehydration peak due to loss of adsorbed water and a subsequent sharp endothermic peak corresponding to fusion of excipient were obtained. Pearlitol, Neosorb, and anhydrous form of dextrose were the only diluents that brought about lowering of ofloxacin melting temperature from 277.37°C to 255.38, 254.98,and as low as 201.78°C thereby affecting the drop in melting point of ofloxacin by 21.99, 22.39, 75.59°C respectively. Neosorb is known to undergo vitrification immediately after fusion 27). The entrapment of drug in the vitrified matrix of neosorb seems to be the probable reason for loss of characteristic melting features of drug and its subsequent appearance at lower temperature (Fig. 3). Inspite of remarkable lowering of ofloxacin melting temperature thermal events unambiguously characteristic of the drug did hardly experience an enthalpy change. As a matter of fact, neither the drug nor the combined system of drug with any of these diluents suffered any enthalpy loss. The concept of enthalpy changes that Shattawy et al. [26] advanced for incompatibility prediction through thermal analysis takes enthalpy change only into account, with absolutely no significance being attached to the temperature shift experienced by the thermal events either of the drug or excipient. If this concept is adopted the thermal changes projected via Fig. 3 do indicate that ofloxacin is more or less equally compatible with Neosorb, Pearlitol, and anhydrous form of dextrose as well. Compatibility ranking both for natural and accelerated temperature storage reveals that Neosorb with respect to its suitability for ofloxacin formulation from chemical compatibility standpoint may occupy any position varying from as best as second and as worst as nine, Pearlitol covering an entire spectrum of ten point scale and dextrose in anhydrous form being almost equally spread from 3 to 9. This suggests that no significant differences could be attached for the compatibility of Neosorb, Pearlitol and dextrose anhyd. with ofloxacin.

The DSC thermogram of lactopress SD and lactochem FP (Fig. 4) revealed two peaks due to loss of bound water and fusion endothermic peak. In presence of ofloxacin, except for each diluent peak located above melting point of the drug that was obliterated, other endothermal features of both these diluents were retained approximately at their original temperatures. The third endothermal character of both these diluents being located around 220°C experienced downward shifts to about 215°C and an additional endothermal event of approximately similar ΔH value of 18-20j/g of the drug and diluent composite having comparable contribution of each of the component were generated in either cases in between 230-240°C at the expense of that endotherm which have been positioned above the melting temperature of the drug. It may be noticed from a glance at Table 4 that the last endothermic peak of drug- diluent system closely approximated penultimate endothermic feature of either diluents. It may be inferred that lactose based diluents brings about complete loss of a single endotherm characterizing the melting process of the drug. Remarkable increase in the heat content (15-200j/g) of the third endotherm of both these diluents located around 200°C suggests melting of diluent in which almost entire amount of the drug not exceeding the amount of diluent got spontaneously dissolved. Lowering of third endotherm of each lactose-based diluent by about 4.4-4.9°C may be attributed to the dissolution of solid-solute drug in molten diluent exhibiting solvent like properties. Enthalpy changes experienced by the drug in contact with these diluents were therefore computed taking the peaks of diluents and composite system located at the temperature above 210°C into an account, while rejecting any thermal event-taking place at the temperature exceeding ofloxacin-melting process.

Enthalpy changes experienced by the drug alone and the complete system summarized in Table 5, along with those brought about by all other diluents reveal that in presence of Lactopress SD, ofloxacin suffered an enthalpy

loss of about 3% and that with Lactochem FP gain of nearly 7 %. However preservation of heat content of entire system, analogous to those encountered in large many cases is indicative of absence of potential incompatibility of ofloxacin with either of the above-mentioned lactose based diluents.

The thermal parameters of ofloxacin, excipients and their binary mixture are listed in Table 4, in the manner such that the endothermal features if retained in binary mixtures (both of drug or diluent) are placed below the thermal feature of diluent and drug respectively. The change observed in enthalpy values with respect to the calculated theoretical values is given in Table 5.

The outcome of this piece of investigation appear to indicate that complete loss of thermal properties of ofloxacin and fusion peak may not necessarily mean an accelerated drug degradation specially when the drug gets dissolved in melted diluent being produced well below the melting point of drug is reached. This could immediately be identified from the changes in thermal properties of the diluent wherein fusion endothermal event of the diluent, apart from the shift of a few degrees to the lower temperature is associated with the gain in enthalpy. It appears that quantum of enthalpy gain provides an idea about the extent to which the drug is able to retain its endothermal fusion event.

Thus the diluents used in the study influenced the thermal behavior of ofloxacin in three characteristic ways: 1. Diluents which retained the endothermal features of drug as such (MCC101, MCC102, Lycatab DCP- anhyd., and Emcompress) 2. Diluents that brought about lowering of endothermal features of drug (Neosorb, Dextrose anhyd., and Pearlitol) 3. Diluents that resulted in loss of endotherm of drug (Lactopress SD and Lactochem FP).

Conclusion

On the basis of initial studies for selecting most appropriate method of sample preparation for isothermal studies, in case of ofloxacin, it was observed that the degradation in the binary mixtures prepared using any of the three methods was not significant enough to classify one method of sample preparation as superior to other. This is probably because stability at the end of the entire study was almost equivalent to 98% indicating compatibility of all the diluents used in combination with drug. From the study it was concluded that a better correlation could have been obtained, had ofloxacin been more unstable with few of the excipients than rest, used in the study. This way the extent of degradation would be distinguishing enough to rank the excipients in decreasing order of stability. In fact designing an experiment wherein the drug is prone to degradation and exhibits incompatibility with the excipients used in a shorter period of time, would go a long way in correlating enthalpy changes with ranking of excipients.

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Table 1 Effect of method of sample preparation on ranking of diluents with ofloxacin in terms of % DR /K values, derived from samples stored at ambient conditions.

Drug/Diluent	P.Ad					Slug					Kneading				
	% DR	Rank	K x 10^5	Rank	*r	% DR	Rank	K x 10^5	Rank	*r	% DR	Rank	K x 10^5	Rank	*r
Ofloxacin(C)	98.30	C	4.61	C	0.97	98.30	C	4.61	C	0.97	98.30	C	4.61	C	0.97
Ofloxacin (R)	100.00	R	4.68	R	0.98	100.00	R	4.33	R	0.97	100.00	R	4.14	R	0.97
MCC101	100.48	1	3.57	2	0.95	100.15	3	4.12	5	0.98	99.90	7	4.31	7	0.99
MCC102	100.41	2	3.32	1	0.99	100.14	4	4.10	4	0.99	99.91	6	4.04	5	0.99
LactochemFP	100.26	3	3.90	3	0.99	99.83	7	4.86	8	0.97	99.77	8	4.76	8	0.98
Dex anhyd.	100.11	4	4.04	4	0.98	99.68	9	4.97	9	0.98	100.03	4	3.82	3	0.99
LactopressSD	99.98	5	4.64	5	0.98	100.01	6	4.03	3	0.98	99.70	9	4.79	9	0.98
Lycatab	99.82	6	5.14	6	0.96	100.16	2	3.76	1	0.95	100.27	1	3.40	2	0.97
Neosorb	99.77	7	5.18	7	0.97	100.10	5	4.20	6	0.98	100.05	3	4.25	6	0.98
DCP-anhyd.	99.67	8	5.40	9	0.98	99.57	10	5.45	10	0.98	100.27	2	3.20	1	0.98
Emcompress	99.66	9	5.23	8	0.96	99.69	8	4.81	7	0.98	99.92	5	4.02	4	0.97
Pearlitol	99.25	10	6.33	10	0.97	100.17	1	3.91	2	0.98	99.63	10	5.30	10	0.98

(C) : Drug control (ofloxacin commercial drug samples as such being used for the study).
(R) : Drug reference (Drug control with 5% w/w added water).
% DR : w. r. t. Drug reference being treated as 100% retained after 6 months.
K : First order decomposition rate constant, day $^{-1}$.
*** r : correlation coefficient [r limiting= 0.924 (n=8 :p<0. 001)].**

Table 2 Effect of method of sample preparation on ranking of diluents with ofloxacin in terms of % DR /K values, derived from accelerated aged samples

Drug/Diluent	P.Ad					Slug					Kneading				
	% DR	Rank	K x 10^5	Rank	*r	% DR	Rank	K x 10^5	Rank	*r	% DR	Rank	K x 10^5	Rank	*r
Ofloxacin(C)	98.43	C	4	C	0.96	98.43	C	4	C	0.96	98.43	C	4	C	0.96
Ofloxacin (R)	100.00	R	5	R	0.98	100.00	R	4	R	0.96	100.00	R	5	R	0.98
MCC101	98.70	1	4	1	0.94	99.87	3	4	3	0.96	100.12	7	5	8	0.97
LactochemFP	98.38	2	4	2	0.96	99.39	9	5	9	0.96	100.16	6	5	4	0.97
MCC102	98.25	3	5	3	0.96	99.79	4	4	4	0.98	100.31	3	4	2	0.94
LactopressSD	98.10	4	5	5	0.94	99.49	7	5	8	0.98	100.33	2	5	5	0.97
Lycatab	98.09	5	5	6	0.93	99.76	5	5	5	0.98	100.03	8	5	7	0.97
Emcompress	98.04	6	5	4	0.96	99.25	10	6	10	0.95	99.81	10	6	9	0.94
Pearlitol	98.02	7	6	8	0.97	100.06	1	4	1	0.98	100.01	9	6	10	0.97
Dex anhyd.	97.90	8	6	7	0.96	99.41	8	5	7	0.98	100.29	4	5	3	0.94
Neosorb	97.90	9	6	9	0.95	99.94	2	4	2	0.97	100.27	5	5	6	0.96
DCP-anhyd.	97.55	10	6	10	0.93	99.56	6	5	6	0.97	100.63	1	4	1	0.90

(C) : Drug control (ofloxacin commercial drug samples as such being used for the study).
(R) : Drug reference (Drug control with 5% w/w added water).
% DR : w. r. t. Drug reference being treated as 100% retained after 6 month
K : First order decomposition rate constant, day $^{-1}$.
*** r : correlation coefficient [r limiting= 0.872 (n=10 :p<0. 001)].**

Table. 3. Stability of ofloxacin in presence of diluents in liquid state (Effect on pH and drug content).

Drug/diluent	pH		Drug content (%)	
	0 hrs	72hrs	0 hrs	48 hrs
Ofloxacin(C)	1.42	1.38	100.00	99.61
MCC101	1.65	1.63	94.98	95.08
MCC102	1.78	1.72	99.87	99.59
DCP-anhyd.	3.02	3.02	99.25	99.01
Emcompress	2.88	2.82	101.00	100.85
Neosorb	1.70	1.74	93.19	92.93
Dex-anhyd.	1.45	1.42	94.12	93.88
Pearlitol	1.72	1.72	93.92	93.72
LactopressSD	1.77	1.72	93.51	93.31
LactochemFP	1.80	1.82	96.95	96.97
Lycatab	1.70	1.76	96.93	96.79

Table. 4. Thermal transitions of ofloxacin, diluents and their 1:1 binary mixtures (Enthalpy change and T_m).

	Excipient								Drug	
	Transition -I		Transition -II		Transition-III		Transition - IV		Transition	
Drug/Diluents	T_m	ΔH	T_m	ΔH	T_m	ΔH	T_m	ΔH	T_m	ΔH
Ofloxacin									277	153
MCC101			74	54						
MCC101+ ofloxacin	56	82							277	141
MCC102			77	49						
MCC102+ofloxacin	56	84							277	143
Lycatab			73	216						
Lycatab +ofloxacin	58	384							277	156
DCP anh.		No transition								
DCPanh.+ofloxacin									278	216
Emcompress			143	34	195	307				
Emcomp+ofloxacin	103	3	142	37	194	354			277	126
Neosorb	101	150								
Neosorb +ofloxacin	100	182	255	185						
Dex. anh.	73	27	156	202						
Dex anh.+ofloxacin	74	65	156	202	202	142				
Pearlitol	168	301								
Pearlitol + ofloxacin	169	300	255	169						
Lactopress SD	149	151	169	1	221 216	149 300	252	86		
Lactopress SD + ofloxacin	150	190	171	9	238	20	256	14		
Lactochem FP	150	155	169	2	219 215	147 348	253	108		
Lactochem FP + ofloxacin	150	201	173	9	231	18	253	23		

Figure. 1. DSC thermograms of ofloxacin (OF) and its (1:1 w/w) binary mixtures with diluents.

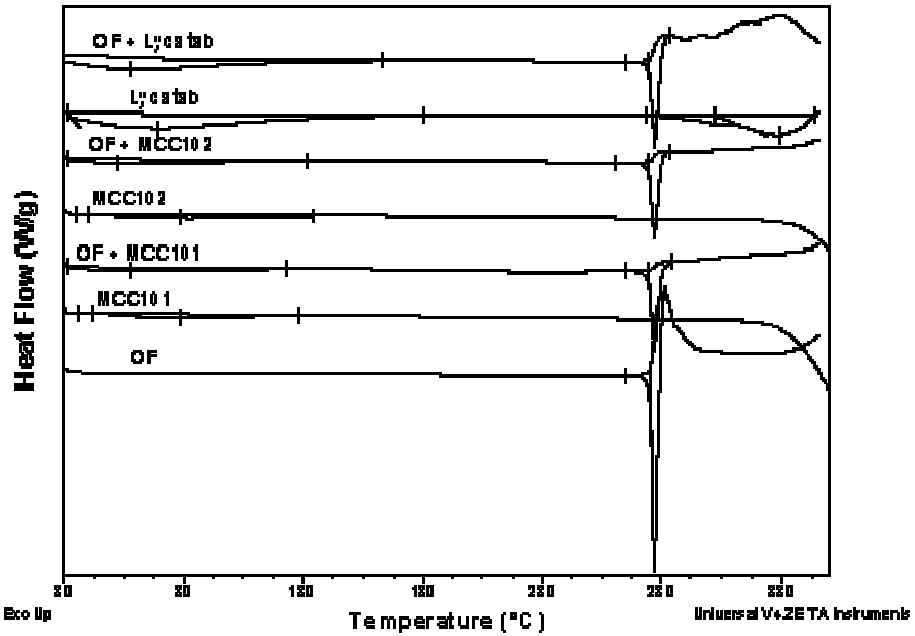

Figure. 2. DSC thermograms of ofloxacin (OF) and its (1:1 w/w) binary mixtures with diluents.

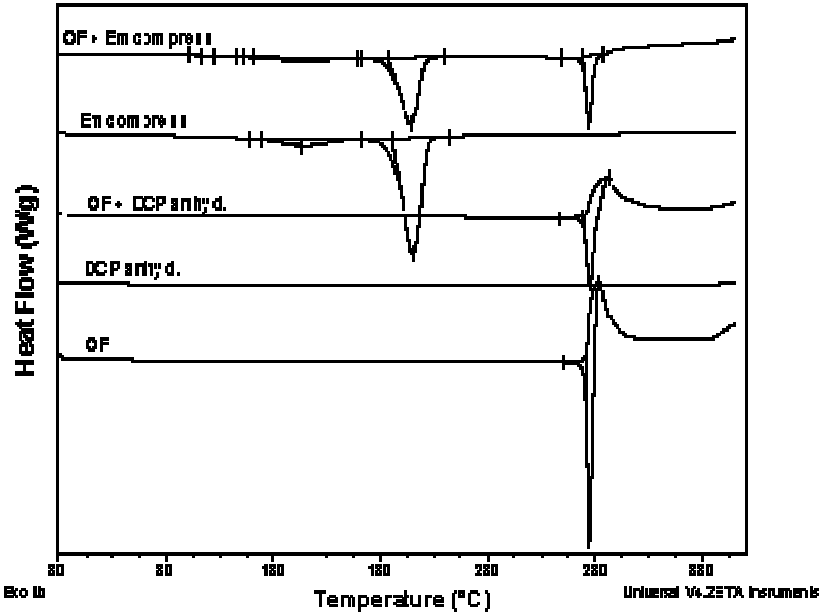

Figure. 3. DSC thermograms of ofloxacin (OF) and its (1:1 w/w) binary mixtures with diluents.

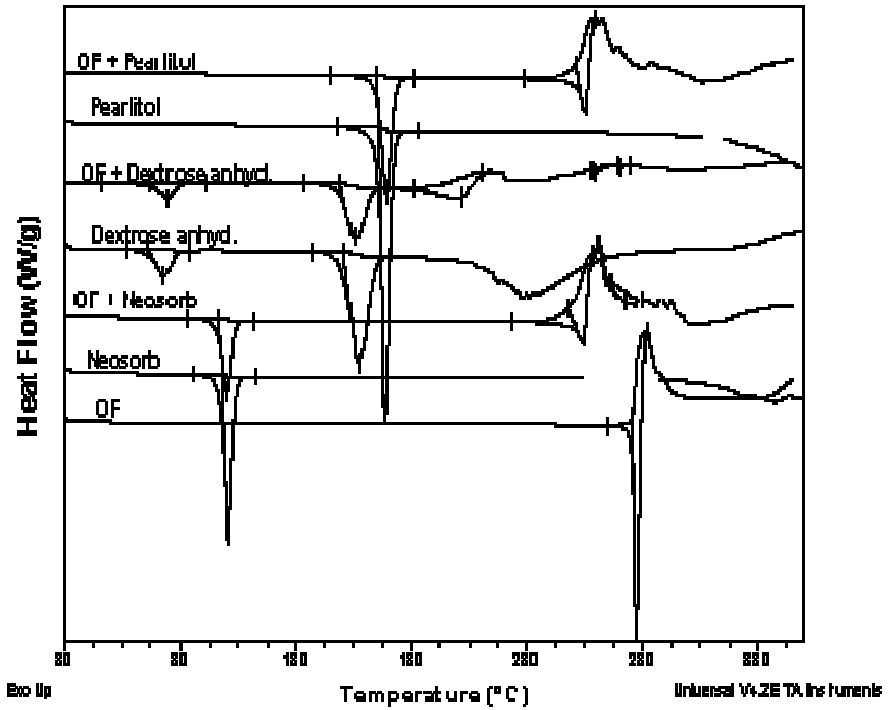

Figure. 4. DSC thermograms of ofloxacin (OF) and its (1:1 w/w) binary mixtures with diluents.