International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.2, No.1, pp 771-783, Jan-Mar 2010

EFFECT OF CO-PROCESSED DIRECT COMPRESSIBLE VEHICLES ON FAST DISSOLVING TABLETS

Niladri Shekhar Dey*, Bibhu Prasad Panda and M.E. Bhanoji Rao

Department of Pharmaceutics, Roland Institution of Pharmaceutical Sciences,

Berhampur, Orissa, India. PIN-760010

Corresponding author: niladrisekhar111@gmail.com

ABSTRACT: The present research work has been carried out for an optimized formulation of co-processed directly compressible vehicles in the preparation of the paracetamol mouth fast dissolving tablets (MFDTs). Paracetamol was chosen due to its poor compression properties. Co-processed direct compressible vehicles such as microcrystalline cellulose spray dried lactose and pearlitol were taken in different ratios such as (10:90, 25:75, 50:50, 75:25 & 90:10) using cross povidone as superdisintegrant. The effects of other superdisintegrants were studied in the best formulation F15. Optimized formulation F15B was found to be optimum compressibility characteristics hardness 4 kg/cm^2 with fast disintegration (9 sec) compare to other formulations.
KEY WORDS: Optimized formulation, poor compression properties, combination ratios, superdisintegrant, compressibility characteristics.

INTRODUCTION

Orodissolving tablets are the dosage forms dissolve or disintegrate in oral cavity within a minute, which significantly increases the bioavailability than those observed from the conventional tablet dosage forms.[1] Several approaches have been employed to formulate fast dissolving tablets involving tablet molding, freeze drying, sublimation, spray drying, disintegrant addition-direct compression and use of sugar based excipients. Out of these, disintegrant addition-direct compression is well known technique where disintegrants help to facilitate drug dissolution and consequently improve the bioavailability. Disintegrants that are effective at lower levels and help in rapid disintegration is of great importance in formulations by direct compression.[2]

Direct compression, over and above eliminates exposure of heat and moisture during processing and is a more economical process. However, the majority of active pharmaceutical ingredients exhibit poor compressibility. Therefore, the addition of directly compressible adjuvant is mandatory. Ideal directly

compressible adjuvant must exhibit good flow ability and compactibility. No single adjuvant is likely to possess all the ideal characteristics. For this reason, the current trend in industry is to use multifunctional co-processed excipients.[3] Nowadays co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible adjuvants. It can be defined as combining two or more established excipients by an appropriate process. Co-processing is based on the novel concept of two or more excipients interacting at the subparticle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual.[4]

Co-processing of excipients could lead to the formation of excipients with superior properties compared to the simple physical mixtures of their

components. The main aim of co-processing is to achieve a product with added value related to the ratio of its functionality price. Development of co-processed directly compressible adjuvant starts with the selection of the excipients to be combined, their targeted proportion, selection of preparation method to get optimized product with desired physicochemical parameters and it ends with minimizing avoidance with batch-to-batch variation. An excipient of reasonable price has to be combined with the optimal amount of a functional material in order to obtain integrated product, with superior functionality than the simple mixture of components. The use of one-body components is justified if it results in a potentiation of the functionalities over that of the dry blend of the functionalities over that of the dry blend of the components prepared by gravity mixture. This synergistic effect should improve the quality of the tablet equally in all aspects ranging from hardness to dissolution and/ or stability.[5] Co-processing is interesting because the products are physically modified in a special way without altering the chemical structure. A fixed and homogenous distribution for the components is achieved by embedding them within minigranules. Segregation is diminished by adhesion of the actives on the porous particles making process validation and in process control easy and reliable.[6] Major limitation of co-processed excipients mixture is that the ratio of the excipients in a mixture is fixed and in the developing a new formulation, a fixed ratio of the excipients may not be an optimum choice for the Active Pharmaceutical Ingredient (API) and the dose per tablet under development.[7]

Present investigation was aimed to prepared paracetamol mouth fast dissolving tablets (MFDTs) using co-processed direct compressible vehicles in different ratios employing direct compression technique to improve hardness, reduce disintegration time as well as to achieve satisfactory mouth feel. Paracetamol an important analgesic and antipyretic agent, was chosen for the present work due to its poor compression properties, and therefore requires a binding agent among other excipients to form good quality tablets.

EXPERIMENTAL

Materials

The drug paracetamol was purchased from Sri Krishna Pharmaceutical & Chemical Ltd., Hyderabad. Microcrystalline cellulose and sodium saccharin was purchased from Loba Chemicals (Mumbai, India). Spray dried lactose and peppermint flavour was purchased from Nihal Pharmaceutical Ltd, (Hyderabad, India) and Ozone International (Mumbai, India) respectively. Pearlitol, sodium starch glycolate, cross carmellose sodium, cross povidone, magnesium stearate and aerosol was procured from SD Fine Chemical, (Mumbai, India).For the present purpose commercial grade co-processed direct compressible vehicles microcellac and starlac was obtained as gift samples from Zydus Cadila Healthcare Ltd. (Amhedabad, India).

Methods

Formulation of paracetamol MFDTs

At first paracetamol mouth fast dissolving tablets (MFDTs) were prepared by direct compression method with different single direct compressible vehicles such as micro crystalline cellulose, spray dried lactose and pearlitol. The co-processed direct compressible vehicles such as micro crystalline cellulose spray dried lactose and pearlitol were taken in different ratios such as (10:90, 25:75, 50:50, 75:25 & 90:10) and cross povidone was taken as superdisintegrants. The effect of other superdisintegrant such as sodium starch glycolate and cross carmellose sodium were studied in best formulation for further achieves optimized formulation. For further optimization study F15B formulation was exposed to experimental design by taking co-processed direct compressible vehicles microcrystalline cellulose with spray dried lactose in slightly different ratios such as 94:6, 92:8, 90:10,88:12 and 86:14 using croscarmelose sodium as superdisintegrant. The comparative study was done between F15b and paracetamol MFDTs by using commercial grade co-processed direct compressible vehicles such as microcellac and starlac. A total number of 26 formulations were prepared. The drug paracetamol were taken 120 mg and mixed with different excipients such as superdisintegrant, magnesium stearate, aerosil, and sodium saccharin, pippermint flavour. All the ingredients were weighed and mixed in simple physical mixing. The tablets were then compressed using 10 mm size flat punches to get a tablet of 300 mg weight using a single punch compression machine (cadmach machinery Pvt. Ltd. Ahmedabad) each batch consists of 50 tablets.

Evaluation of mouth fast dissolving tablets

The tablets were characterized for drug content uniformity, weight variation, hardness, disintegration time, dispersion time, wetting time, water absorption ratio, friability, mouth feel and in vitro dissolution study.

Drug content uniformity

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and extracted in phosphate buffer pH 6.8 and concentration of drug was determined by measuring absorbance at 245 nm by UV spectrophotometer (Model UV-2401, Shimadzu).[8]

Weight variation

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.[9]

Hardness of tablets

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.[10]

Friability test

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again.[11] The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula

$$\% \text{ friability} = [(W1-W2)100]/W1 \quad (1)$$

Where,

W1= Weight of tablet before test

W2 = Weight of tablet after test

Disintegration test

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2 ^{o}C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker.[12]

Uniformity of dispersion

Two tablets were kept in 100ml water and gently stirred for 2 minutes. The dispersion was passed through 22 meshes. The tablets were considered to pass the test if no residue remained on the screen.[13]

Wetting Time

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a Petri dish containing 0.2% w/v solution (3ml) a tablet was carefully placed on the surface of the tissue paper. The time required for develop blue colour on the upper surface of the tablets was noted as the wetting time.[14]

Water Absorption Ratio

A small piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then reweighed.[14] Water absorption ratio, R was determined by using following formula were given

$$R= 100 \times W_a-W_b / W_b \quad (2)$$

W_b is the weight of tablet before water absorption

W_a is the weight of tablet after water absorption

Taste/ Mouth sensation

Mouth-feel is critical, and patients should receive a product that feels pleasant. One tablet from each batch was tested for the sensation by placing the tablet on the tongue. The healthy human volunteers were used for evaluation of taste masking and the feed back was obtained from all of them. Taste evaluation was done by a panel of 10 members using time intensity method. Sample equivalent to 5 mg i.e. dose of drug was held in mouth for 10 sec. Bitterness levels were recorded instantly and then after 10 sec, 1,2,4,6 and 8 minutes. Volunteer's option for bitterness values were rated by giving different score values that is 0: no bitterness, 1: acceptable, 2: slightly bitter, 3: moderately bitter, 4: strongly bitter.[14]

In vitro dissolution tests

The paracetamol fast dissolving tablets were subjected to in vitro drug release studies in pH 6.8 phosphate buffer for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in eight stage dissolution test apparatus (DISSO 2000, Lab India) using 900 ml of dissolution medium (pH 6.8 phosphate buffer) maintained at 37±1^{0}C. The tablets were kept in the cylindrical basket and rotated at 100 rpm. 5ml of the sample from the dissolution medium were withdrawn at each time interval (2, 3, 5, 10, 15 and 30 minutes) and 5ml of fresh medium was replaced each time. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml with pH 6.8 Phosphate buffer. The absorbances of the sample were measured at λ max 245 nm using UV spectrophotometer.[15]

In-vitro dissolution kinetic studies

The drug release data were plotted and tested with zero order (cumulative % drug released Vs time), First order (Log % remained Vs time). The in vitro dissolution kinetic parameters, dissolution rate constants (K), correlation coefficient (r), the times (t_{50}) for 50 % drug released (half-life) and dissolution

efficiency [D.E.] were calculated. From the slopes of linear plots, the dissolution rates were calculated.[16]

Kinetics of drug release (First-order release kinetics)

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t / 2.303 \quad (3)$$

The first-order equation describes the release from systems where release rate is concentration dependent. Where Q_0 is the initial amount of the drug, t is in minutes and K_1 describes the dissolution rate constant for first order release kinetics. A plot of the logarithm of the percent drug remained against time will be linear if the release obeys first- order release kinetics. Values of release rate constant K_1 are obtained in each case from the slope of the log % drug remained versus time plots.

The correlation coefficient between the time and cumulative amount of drug released were also calculated to find the fitness of the data to zero order kinetics. A zero- order dissolution profile can be described by the following mathematical model.

$$Q_t = Q_0 + K_0 t \quad (4)$$

Where, Q_t is the amount of drug released (and dissolved) in time t, 0 is the initial amount of drug in the solution (in most cases Q_0) and K_0 is the zero-order release constant.[17]

Dissolution Efficiency (DE)

The dissolution profiles are evaluated on the basis of dissolution efficiency (DE) parameter at 100 min and the dissolved percentage (DP) at 100 min. DE is defined as the area under the dissolution curve up to the time "t" expressed as a percentage of the area of the trapezoid described by 100% dissolution in the same time.

$$\text{Dissolution Efficiency (DE)} = \left({}^{t}\int_0 y\, dt / y_{100}\, t\right) 100 \quad (5)$$

The dissolution efficiency can have a range of values depending on the time interval chosen. In any case constant time intervals should be chosen for comparison. For example, the index DE_{30} would relate to the dissolution of the drug from a particular formulation after 30 minutes could only be compared with DE_{30} of after formulations.[18]

Comparison of Dissolution Profile

1. Determine the dissolution profile of two products (12 units each) of the test (postchange) and reference (prechange) products.

2. Using the mean dissolution values from both curves at each time interval, calculate the difference factor (f_1) and similarity factor (f_2) using the above equations.

3. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100)

ensure sameness or equivalence of the two curves and, thus, of the performance of the test (post change) and reference (pre change) products.[19]

Analysis of Variance (ANOVA)

One way analysis of variance (ANOVA) compares the means of three or more groups. The null hypothesis is that all column means are equal and P value testing this null hypothesis. The one way ANOVA test assumes that data are randomly sampled from larger populations (or at least are representative of those populations) that each value was obtained independently of others, that the populations are scattered accordingly to a Gaussian distribution, and that the SD of the two populations are equal. It shows intermediate calculations that lead to calculate F value. If the calculated value is less than tabulated value, it can be concluded that the data are unlikely to be sampled from populations with equal means.[20]

Stability Study

Ten tablets of optimized formulation were placed in petri dish, which was kept in a desiccators containing calcium chloride (desiccant) at room temperature for one day. The tablets were then weighed and placed in humidity chamber, which was maintained at 40°C/75% RH for one month. The physical characteristics like weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time, mouth feel and in-vitro drug release profile were determined at interval of 15 and 30 days and results were recorded.[21]

RESULTS AND DISCUSSION

Paracetamol MFDTs were developed and it was modified further to get a suitable basic formula. At first three different direct compressible vehicles were taken such as microcrystalline cellulose (MCC), spray dried lactose (SPDL), pearlitol (PL) and cross povidone (CPV) as superdisintegrant was used for the formulation of paracetamol MFDTs (Table 1). All tablets were evaluated for content uniformity, weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time, dispersion time and mouth feel (Table2). Formulation FA (paracetamol with MCC) shows hardness 3 kg/cm^2 and disintegration time 45 sec. FB (paracetamol with spray dried lactose) shows hardness 2.1kg/cm^2 and disintegration time 30 sec where as formulation FC (paracetamol with pearlitol) shows hardness 2.3 kg/cm^2 and disintegration time 28 sec. Among them formulation FA shows better hardness and disintegration time 45 sec fulfilling the official requirements for a MFDTs.

Study the effect of co-processed direct compressible vehicles on fast dissolving tablets

For present research it was formulated with the co-processed direct compressible vehicles microcrystalline cellulose, spray dried lactose and pearlitol in different ratios such as 10:90, 25:75, 50:50, 75:25 and 90:10 (Table 1) and their evaluation, results were obtained and (Table 2).Drug content uniformity all formulations in range of 95 to 99% within in specified limit. The formulations F1 to F5 (spray dried lactose with pearlitol) shows hardness in range of 2.5 to 3.5 kg/cm^2 and disintegration time in range of 18 to 30 sec. Among them formulation F2 (SPDL: PL 25:75 with CPV) shows better hardness like 3.5 kg/cm^2, disintegration time 25 sec. The formulations F6 to F10 (pearlitol with microcrystalline cellulose) shows hardness in range of 3.0 to 4.0 kg/cm^2 and disintegration time in range of 15 to 58 sec. Among them formulation F9 (PL: MCC 75:25 with CPV) shows better hardness like 4 kg/cm^2, disintegration time 28 sec. The formulations F11 to F15 (microcrystalline cellulose with spray dried lactose) shows hardness in range of 3.5 to 4.5 kg/cm^2 and disintegration time in range of 23 to 28 sec. Among them formulation F15 (MCC: SPDL90:10 with CPV) shows better hardness like 4 kg/cm^2 and disintegration time 23 sec. In-vitro dissolution study was performed for these four formulations in respect of pH 6.8 phosphate buffer with comparison of marketed product of paracetamol dispersible tablets (P250). Among them F15 formulation (MCC: SPDL 90:10 with CPV) shows maximum drug release of 95.63 % within 30 minutes followed by marketed product 95.43 % drug releases (Figure 1). Kinetic study was done for the selected formulations; it was found that drug release followed first order release kinetics. F15 shows t ½ 6.68 sec, DE_{30} 66.38% and K_1 0.103 min^{-1} (Table 3).

Study the effect of various superdisintegrants on selected formulations

The effect of other superdisintegrants such as sodium starch glycolate and crosscarmellose sodium was studied on the selected formulation F15 (Table 1). All tablets were evaluated (Table 2). Drug content uniformity all formulations in range of 99 to 102 % within in specified limit. Among the three formulations F15, F15A and F15B shows same hardness such as 4kg/cm^2 and disintegration time 23, 22 and 9 sec respectively. The disintegration time is represented in bar diagram (Figure 3).

Comparison of disintegration time using various superdisintegrants

In-vitro dissolution study was carried out for these three formulations in pH 6.8 phosphate buffer. F15B shows maximum drug release that is 98.43% within 30 minutes where as F15 and F15A shows drug release 95.63 and 96.09% respectively within 30 minutes (Figure 4).

Kinetic study was done for all formulations; it was found that drug release followed first order release kinetics. F15B shows t ½ 4.94 sec, DE_{30} 73.25 % and K_1 0.140 min^{-1} (Table 3). So F15B formulation was selected.

Development of fast dissolving tablets by experimental design

For further optimization study F15B formulation was exposed to experimental design. Here co-processed direct compressible vehicles microcrystalline cellulose with spray dried lactose were taken in slightly different ratios such as 94:6, 92:8, 90:10,88:12 and 86:14 using croscarmelose sodium as superdisintegrant (Table 1). All the tablets were evaluated (Table 2). Drug content uniformity all formulations in range of 97 to 102 % within in specified limit. All the formulations showed hardness 4kg/cm^2 but F15B shows less disintegration time that is 9 sec. All the disintegration time is represented in bar diagram (Figure 6).In-vitro dissolution study was carried out for above formulations with respect of pH 6.8 phosphate buffer. Among them F15B again shows maximum drug release that is 98.43% within 30 minutes compare to other formulations (Figure 7). Kinetic study was done for all formulations; it was found that drug release followed first order release kinetics. F15B further shows t ½ 4.94 sec, DE30 73.25 % and K1 0.140 min^{-1} (Table 3). So F15B formulation was finally selected.

One way ANOVA was applied to the selected formulations FA, F15B and marketed product paracetamol dispersible tablets (P250) taking disintegration time under consideration (Table 4). The calculated value was greater than table value (Table 5).

Study the effect of co-processed direct compressible vehicles (commercial grade) in fast dissolving tablets

Further the comparative study has been carried out for formulation F15B with commercial grade co-processed direct compressible vehicles such as microcellac and starlac on paracetamol MFDTs with superdisintegrant cross carmellose sodium. Microcellac and starlac were taken as co-processed direct compressible vehicles. Among them F20 (microcellac) and F21 (starlac) shows hardness 3.5 and 3 kg/cm^2 where as disintegration time 31 and 46 sec respectively and drug content uniformity of all formulations in range of 99 to 102 % which is in specified limit (Table 2). All the

disintegration time is represented in bar diagram (Figure 9).

Comparison of disintegration time of optimized formulation with marketed co-processed direct compressible vehicles

In-vitro dissolution study was carried out for F15B, F20 and F21 with respect of pH 6.8 phosphate buffer. Among them F15B shows maximum drug release that is 98.43% within 30 minutes compare to F20 and F21 as indicated in **(**Figure 10). Kinetic study was done for all formulations; it was found that drug release followed first order release kinetics. F15B further shows t ½ 4.94 sec, DE_{30} 73.25 % and K_1 0.140 min^{-1} (Table 3). So F15B formulation was finally optimized.

Similarity factor and dis-similarity factorfor in vitro drug release profile

Applying F test (f_1 and f_2) under appropriate conditions. The in-vitro release profile of optimized formulation (F15B) and marketed product. In pH 6.8 phosphate buffer were compared for dis-similarity factor f_1 and similarity factor f_2. The values f_1 6.88 and f_2. 78.26 shows there is similarity between both the drug release profiles (Table 6)

Drug- excipient interaction studies

Identical IR spectra were obtained for optimized formulation (F15B) when compared with pure drug paracetamol. There was no appearance of new peaks or disappearance of characteristics peaks, which confirmed the absence of chemical interaction between the drug and excipients. FTIR studies indicated that paracetamol does not form any interaction with excipients like microcrystalline cellulose, spray dried lactose and cross carmellose sodium (Figure 12 and 13).

Stability Studies

The stability studies of the optimized formulation F15B was carried out for 30 days. There was no significant change in drug content as well as physical parameters such as weight variation, hardness, friability, wetting time, water absorption ratio, appearance and in-vitro dissolution test during stability study (Table 7 and Figure 14).

CONCLUSION

A basic formula consisting microcrystalline cellulose, spray dried lactose and pearlitol were used as single direct compressible vehicles and cross povidone as superdisintegrant. The co-processed direct compressible vehicles in different combination ratios were used for investigation in the formulation of paracetamol MFDTs. Among them F15 formula shows less disintegration time 23 sec and hardness of 4 kg/cm^2. After study with various superdisintegrants in F15 formula it was seen that F15B formulation (MCC: SPDL 90:10 with CCS) were having less disintegration time 9 sec and hardness of 4 kg/cm^2. From the experimental design F15B was further found to be optimum and also satisfies the basic requirements such as hardness of 4 kg/cm^2 and disintegration time of 9 sec and satisfactory mouth feel.

F15B further shows better hardness as well as less disintegration time compared to commercial grade co-processed direct compressible vehicles such as microcellac (F20) and starlac (F21). In FTIR spectra indicates that there was no interaction within drug and excipients. The tablets of optimized formulation was exposed to short term stability study for one month and it was found that there was no significant change in drug content as well as the physical parameters and appearance. Co-processed direct compressible vehicles produce synergistic effect in terms of compressibility and can help improve functionalities such as compaction performance, hardness and short disintegration time.

Table 1. Formulations of Paracetamol MFDTs

*Formulation	Ingredients (mg)								
	Paracetamol	Super-disintegrant	MCC	SPDL	PL	Magnesium sterate	Aerosil	Peppermint flavour	Sodium Saccharin
FA	120	9	156	------	----	3	3	3	6
FB	120	9	------	156	-----	3	3	3	6
FC	120	9	------	------	156	3	3	3	6
F1	120	9	-------	15.6	140.4	3	3	3	6
F2	120	9	-------	39	117	3	3	3	6
F3	120	9	--------	78	78	3	3	3	6
F4	120	9	------	117	39	3	3	3	6
F5	120	9	--------	140.4	15.6	3	3	3	6
F6	120	9	140.4	-------	15.6	3	3	3	6
F7	120	9	117	------	39	3	3	3	6
F8	120	9	78	------	78	3	3	3	6
F9	120	9	39	------	117	3	3	3	6
F10	120	9	15.6	-------	140.4	3	3	3	6
F11	120	9	15.6	140.4	-----	3	3	3	6
F12	120	9	39	117	-----	3	3	3	6
F13	120	9	78	78	--------	3	3	3	6
F14	120	9	117	39	------	3	3	3	6
F15	120	9	140.4	15.6	------	3	3	3	6
F15A	120	9	140.4	15.6	--------	3	3	3	6
F15B	120	9	140.4	15.6	-------	3	3	3	6
F16	120	9	146.64	9.36	------	3	3	3	6
F17	120	9	143.52	12.48	-------	3	3	3	6
F18	120	9	137.28	18.72	-------	3	3	3	6
F19	120	9	134.16	21.84	--------	3	3	3	6

MCC-Microcrystalline cellulose, SPDL-Spray Dried lactose, PL-Pearlitol

* Each batch consists of 50 tablets, each tablet weight-300mg

Table 2. Evaluation Parameter of Paracetamol MFDTs

Formulation	Parameters								
	Drug content uniformity (%)	Weight variation (±)	Hardness (kg/cm^2)	Friability (% loss)	Wetting time (sec)	Water absorption ratio (R)	Disinegration time (sec)	Dispersion time (sec)	Mouth feel
FA	97	0.33	3.0	0.23	25	101.6	45	40	3
FB	96	0.98	2.1	0.92	20	58.46	30	33	2
FC	96	0.96	2.3	0.87	20	60.92	28	30	2
F1	96	0.87	2.5	0.30	28	18.275	30	35	0
F2	97	0.73	3.5	0.35	20	63.680	25	20	0
F3	95	0.71	3.0	0.62	20	57.760	30	28	0
F4	97	0.89	2.5	0.97	15	61.560	35	32	0
F5	98	0.83	2.5	0.90	12	45.328	18	25	0
F6	98	0.98	3.5	0.95	10	43.150	15	20	1
F7	97	0.91	3.5	0.92	13	41.379	18	25	1
F8	98	0.89	4.0	0.98	25	52.920	58	40	1
F9	99	0.88	4.0	0.90	12	38.013	28	30	1

F10	97	0.87	3.0	0.93	12	38.983	20	40	1
F11	98	0.83	3.5	0.91	14	43.298	26	20	1
F12	96	0.87	4.0	0.90	18	40..689	25	30	1
F13	97	0.89	4.5	0.89	20	44.827	28	25	1
F14	98	0.91	4.0	0.87	17	46..084	24	30	1
F15	99	0.92	4.0	0.91	20	52.218	23	30	1
F15A	101	0.88	4.0	0.93	18.6	56.134	22	20	1
F15B	102	0.89	4.0	0.92	8.0	51.430	9	12	1
F16	97	0.91	4.0	0.95	17	47.789	21	18	1
F17	98	0.93	4.0	0.94	12	53.934	18	15	1
F18	99	0.89	4.0	0.97	9	44.843	12	10	1
F19	98	0.88	4.0	0.92	10	51.923	14	11	0
F20	98	0.88	3.5	0.97	31	39.54	42	39	1
F21	99	0.84	3.0	0.95	46	47.93	58	51	1

Table 3. Kinetic study paracetamol MFDTs

Product code	**Time Vs % drug release**			**Time Vs Log % drug release**				**DE_{30} (%)**
	slope	**R**	**K_o (mg/ml min^{-1})**	**slope**	**R**	**K_1 (min^{-1})**	**t ½ (hrs)**	
FA	2.657	0.93	2.657	0.026	0.99	0.061	11.2	60.76
F2	2.881	0.94	2.881	0.030	0.99	0.070	9.76	59.46
F9	3.004	0.95	3.004	0.038	0.99	0.087	7.89	61.53
F15	3.017	0.93	3.017	0.045	0.99	0.103	6.68	66.38
MP	3.044	0.90	3.044	0.044	0.99	0.102	6.73	69.12
F15A	3.022	0.93	3.022	0.046	0.99	0.107	6.44	68.02
F15B	3.111	0.89	3.111	0.060	0.99	0.140	4.94	73.25
F16	3.070	0.97	3.070	0.036	0.99	0.084	8.19	56.53
F17	3.018	0.96	3.018	0.036	0.99	0.084	8.17	58.56
F18	3.115	0.92	3.115	0.050	0.99	0.116	5.93	67.66
F19	3.107	0.93	3.107	0.047	0.99	0.109	6.34	66.72
F20	3.258	0.94	3.258	0.047	0.99	0.108	6.36	63.76
F21	3.237	0.95	3.237	0.043	0.99	0.101	6.85	60.59

Table 4. Disintegration time of formulations of FA, F15B and marketed product

Sample number	**Different formulations of paracetamol MFDTs**		
	FA	**F15B**	**Marketed product (P 250)**
1	45.0	9.5	48.0
2	42.5	9.0	48.2
3	43.2	9.2	48.3
4	44.9	9.6	48.1
5	43.3	9.1	48.3

Table 5. One way ANOVA table

Source of variation	Degree of freedom	Sum of Squares	Mean Squares	F Calculated Value	F Table value
Between the formulations	2	4538	2269	5153	for 0.01=6.93 & for0.05=3.89
Within the formulations	12	5.284	0.4403		
Total	14	4543			

Table 6. Calculation of Similarity factor (f2) and Dis-similarity factor (f1) between F15B and marketed product (P250)

Time (minitues)	F15B	Marketed product (P 250)
2	18.01	16.32
3	31.78	26.87
5	46.34	43.36
10	72.98	68.91
15	85.76	79.67
30	98.43	95.43
Dis-similarity factor (f1) =6.88 Similarity factor (f2) =78.26		

Mean of 12 units of marketed dispersible tablet of paracetamol

Table 7. Evaluation of optimized formulation during stability study period (40^{o}C/75%RH)

Parameters	0 day	15 days	30 days
Drug content uniformity (%)	102	102	102
Weight variation (±)	0.89	0.90	0.91
Hardness (kg/cm^2)	4.0	4.2	4.4
Friability (% loss)	0.92	0.93	0.95
Wetting time (sec)	8.9	8.7	8.6
Water absorption ratio(R)	51.431	51.542	52.345
Disintegration time (sec)	9.0	9.2	10.4
Dispersion time (sec)	12.0	13.1	13.6
Moisture uptake (% increasing weight)	2.0	2.1	2.4
Mouth feel	1	1	1

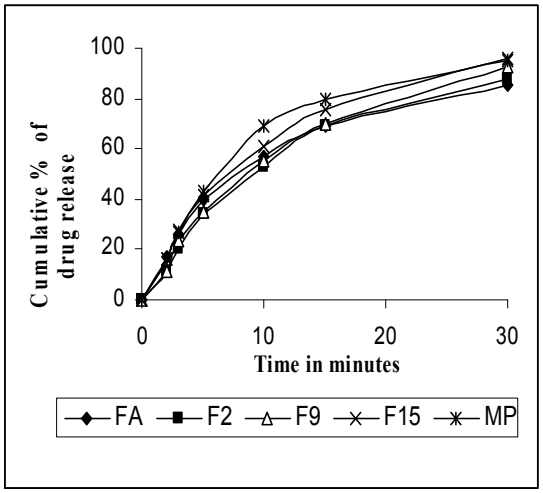

Figure1. In vitro release profile of paracetamol MFDTs

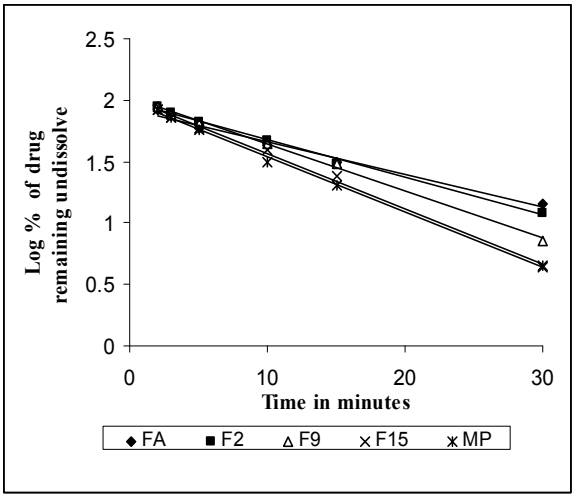

Figure 2. Log % of drug retained of paracetamol MFDTs

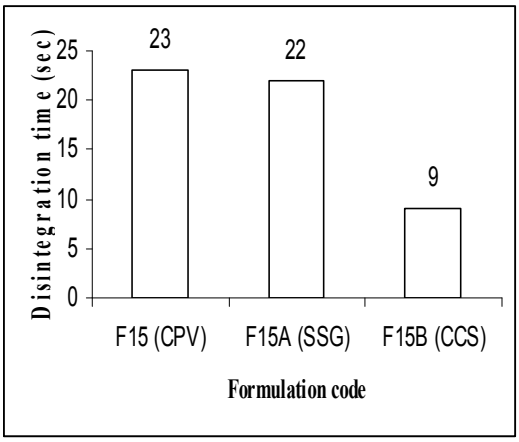

Figure 3. Comparison of disintegration time using various superdisintegrants

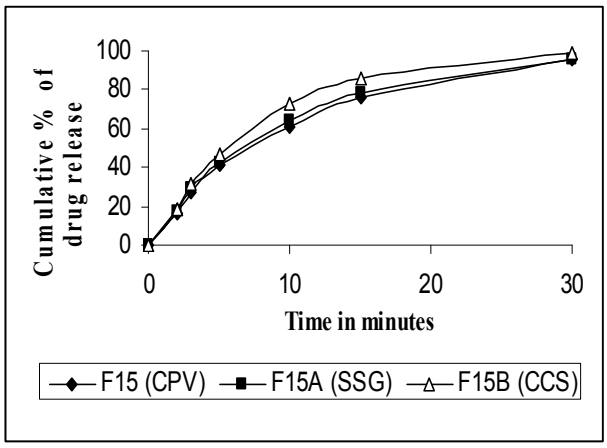

Figure 4. In vitro release profiles MFDTs using various superdisintegrants

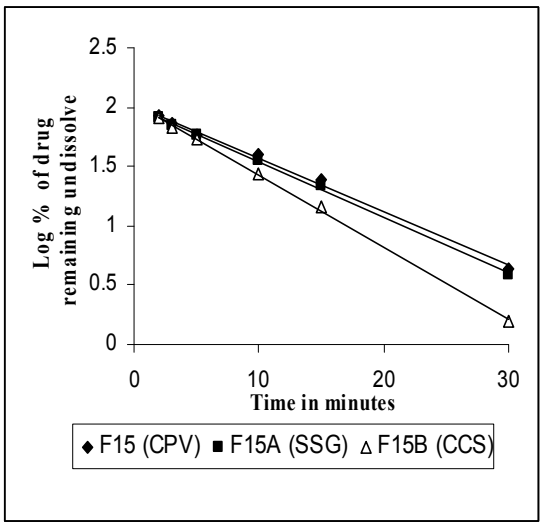

Figure 5. Log % of drug retained

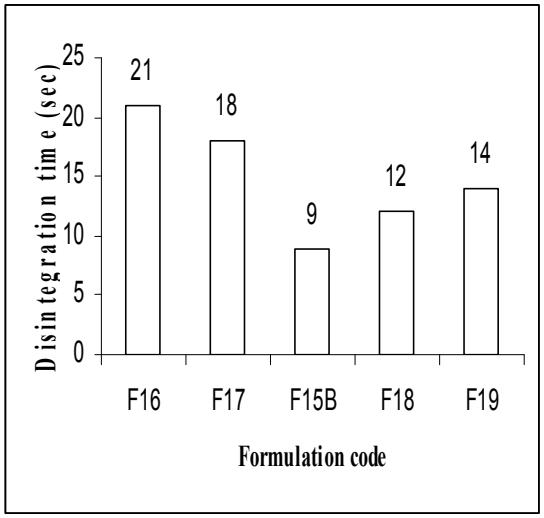

Figure 6. Comparison of disintegration time by experimental design

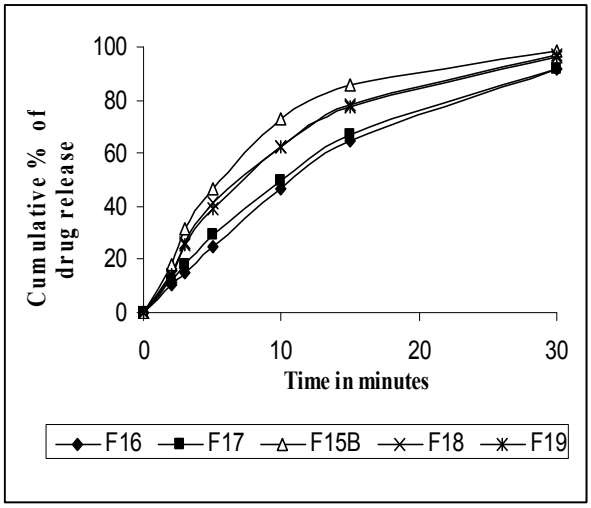

Figure 7. In vitro release profiles of experimental design

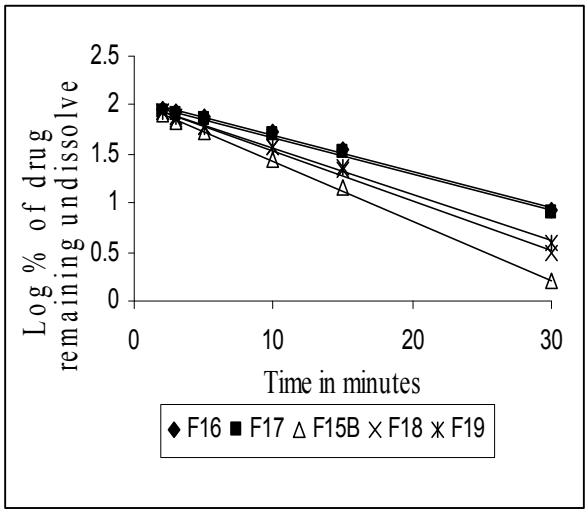

Figure 8. Log % of drug retained paracetamol MFDTs in in experimental design

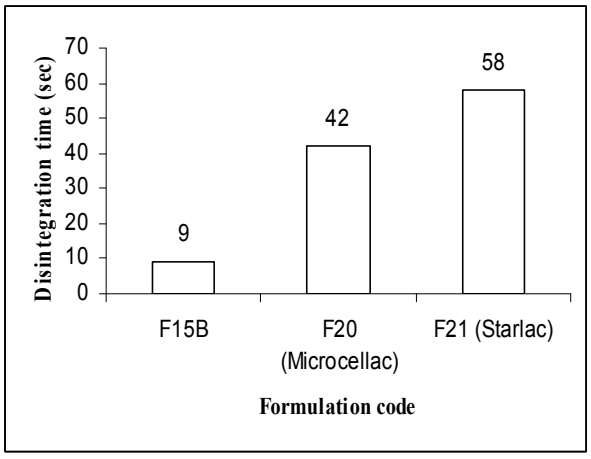

Figure 9. Comparison of disintegration time

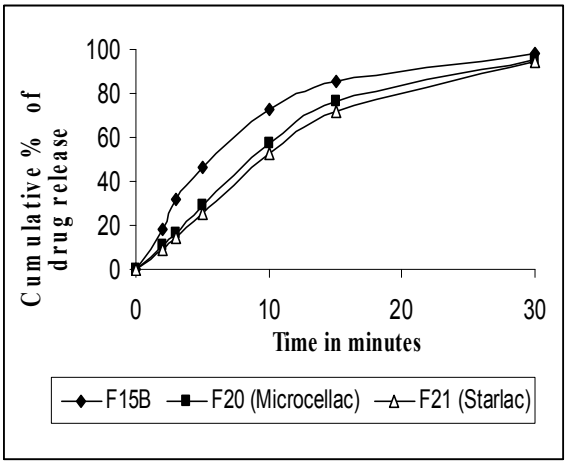

Figure 10. In vitro drug release profile

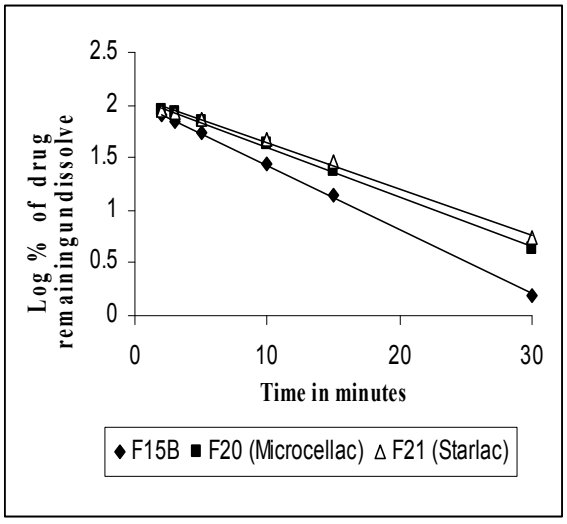

Figure11.Log % of drug retained

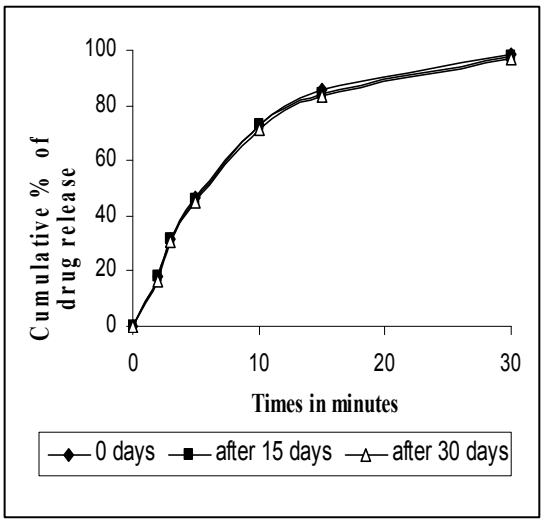

Figure 12. FTIR study of pure drug paracetamol

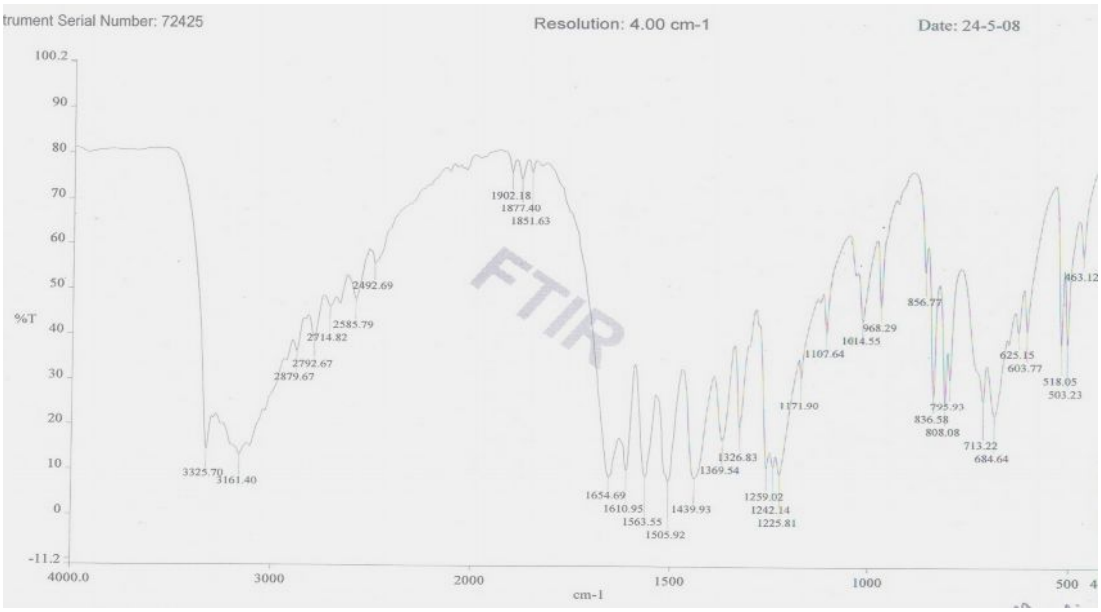

Figure 13. FTIR study of optimized formulation F15B

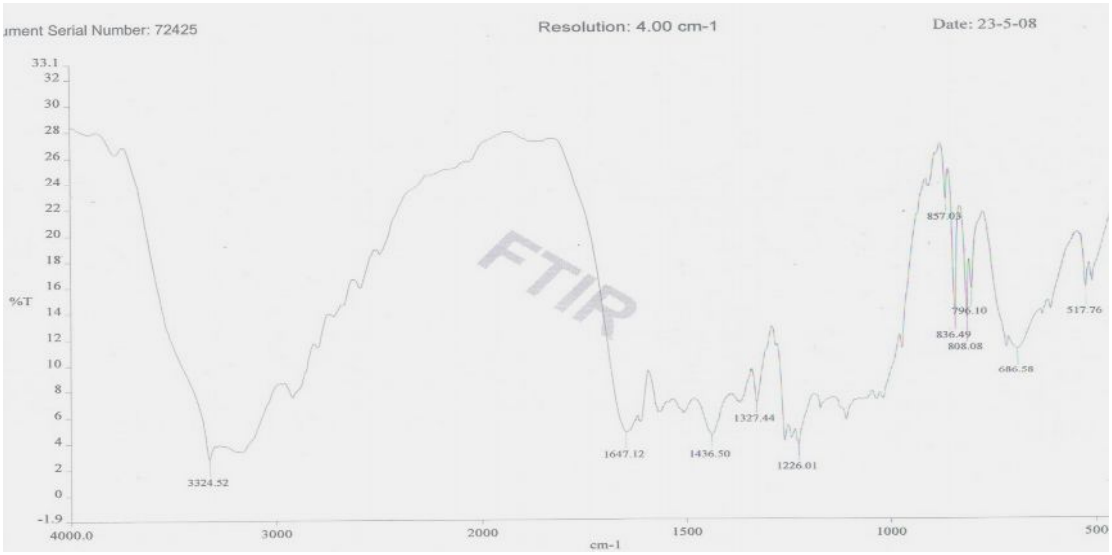

Figure 14. In vitro release profiles

Acknowledgements

The authors thank Zydus Cadila Healthcare Ltd., Amhedabad for providing samples of commercial grade co-processed direct compressible vehicles microcellac and starlac. Thanks are also to Shipra Laboratory for carry out FTIR studies of pure drug and optimized formulation.

REFERENCES

1. Mahajan, H.S., Kuchekar, B.S., Badhan, A.C. Mouth dissolve tablets of sumatriptan succinate. Indian J Pharm Sci 2004**;** 66: 238-240.
2. Seager, H. Drug delivery products and zydus fast dissolving dosage form. J.Pharm. Pharmacol 1998, 50: 375-378.
3. Patel, S.S. Patel, N.M. Recent trends in direct compression technology. Pharma Buzz 2007, 2: 24-34.
4. Reimerdes, D. The near future of tablet excipients. Manuf Chem. 1993, 64:14-15.
5. Jacob, S., Shirwaikar, A.A., Joseph, A., Srinivasan, K.K. Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast dissolving tablets of glipizide. Indian J. Pharm.Sci. 2007, 69:633-639.
6. Russel, R. Synthetic excipients challenge all-natural organics offer advantages challenges to developers and formulators. Pharm. Technol. 2004, 27:38-50.

7. Nachaegari, S.K., Bansal, A.K. Co-processed excipients for solid dosage forms. Pharmaceutical Technology 2004, 28:52-64.
8. The United States Pharmacopoeia 27th Revision and the National Formulary 22nd Ed. The official compendia of standards. Asian Edition. Published by the Board of Trustees. 2004, pp 776-777.
9. Lachman, L., Lieberman, HA., Kanig JL. Tablets. Banker, G.S., Anderson, N.R. The Theory and Practice of Industrial Pharmacy. 3rd edition. Lea and Febiger Varghese Publishing House, Dadar, Bombay, India, 1987, Chapter 11, pp 293-345.
10. Goodhart, F.W., Draper, J.R.., Dancz, D., Ninger, F.C. Evaluation of tablet breaking strength testers. J.Pharm Sci. 1973, 62: 297-304.
11. Indian Pharmacopoeia, Government of India. Ministry of Health and Family Welfare. Published by the controller of publications. Delhi, India, 1996, Vol.1, pp 80-81.
12. Dandagi, P.M., Sreenivas, S.A., Manvi, F.V., Patil, M.B. Taste masked ofloxacin mouth disintegrating tablets. Ind. Drugs. 2005, 42: 52-55.
13. Bi, Y.X., Sunada, H., Yonezawa, Y., Danjo, K. Evaluation or rapidly disintegrating tablets prepared by a direct compression method. Chem Pharm Bull. 1996, 44: 2121-2125.
14. Chaudhari, P.D., Kolhe, S.R., Dave, K.V., More, D.M. Formulation and evaluation of fast dissolving tablets of famotidine. Indian Drugs. 2005, 42:641-649.
15. Khan, K.A. In vitro dissolution rate studies and dissolution efficiency. J. Pharm. Pharmacol. 1975, 27:48-49.
16. Costa, P., Lobo, J.M.S. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 2001, 13:123-133.
17. Mehuys, E. Development of a matrix-in-cylinder system for sustained zero order drug release. Laboratory of Pharma Technol. 2004, 13: 39-40.
18. Peppas, N.A. Analysis of fickian and non-fickian drug release polymers. Pharm. Acta. Helv. 1985, 60:110-111.
19. Moore, J.W., Flanner, H.H. Mathematical comparison of curves with an emphasis on in-vitro dissolution profiles. Pharm. Tech. 1996, 20**:**64-74.
20. Gupta SP. Statistical Methods, 34 th edition. S. Chand publication, New Delhi, India 2005, Vol.2, pp. 1009-1018.
21. Remington. Stability of Pharmaceutical Products, Vadas E.B., The Science and Practice of Pharmacy, 20th edition, Lippincott Williams and Wilkins publication. 2000, Vol.1, Chapter 52, pp. 986-994.

*****