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Research Article

Formulation Development and Evaluation of Metformin Hydrochloride Extended Release Tablets

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ABSTRACT
Extended release tablets of Metformin HCl were developed due to lower half-life, high solubility and less bioavailability. The tablets were prepared by hydrophilic matrix technique and combination of hydrophilic matrix with hydrophobic coating as reservoir. Hypromellose was used as matrixing agent and ethyl cellulose as hydrophobic coating material. In vitro dissolution studies of optimized, F3a (3% coated) formulation showed satisfactory results for f2 and f1 values i.e 80.29 and 2.87 respectively. And the dissolution profile was almost similar with that of reference product. The results of the dissolution study were examined according to Zero, First and Higuchi model as shown for reference product. The regression coefficient (R^2) value obtained from the log %ARR (Amount Remaining to Release) versus time was 0.9396 which is nearer to 1, indicating first order release for formulation F3a.
Results of stability study carried out on formulation F3a for three months indicated that, there was no any significant change in drug release of the tablet as well as % assay results were found within specifications. Hence, the optimized formulation was stable.

Keywords: Type II diabetes, Hypromellose, Extended release, Metformin HCl, Matrix tablets

INTRODUCTION

Diabetes mellitus is a major and growing public health problem throughout the world. Recent estimates project that the number of patients diagnosed with type II diabetes will more than double to 300 million before 2025. [1]Maintaining normal plasma glucose levels is a key factor in reducing the risk of developing diabetes complications. [2,3] Metformin is a biguanide antihyperglycemic agent used in the treatment of non-insulin dependent diabetes mellitus (NIDDM).

In spite of its favorable clinical response and lack of significant draw backs, chronic therapy with metformin hydrochloride suffers from certain problems. The marketed immediate release products need to be administered 2-3 times daily. The current metformin therapy is associated with high incident of GI side effects seen in about 30% of patients. [4] Moreover inherent compressibility, very high solubility (i.e. >300 mg/ml at 25° C), initial burst effect of drug from immediate release tablets and less bioavailability (60%) due to saturable absorption process can lead to difficulty in providing an optimum therapeutic effect from a formulation.

So, the attempts were made to formulate an extended release drug delivery system that has a longer transit time in the stomach and acts as an in vivo reservoir that releases drug at a controlled rate continuously over a prolonged time for absorption in the stomach and the intestine. Various studies and literatures reported the use of HPMC matrices and ethyl cellulose to control the release of variety of drug from matrices.

As extended release tablets offers several advantages over conventional therapy, it is proposed in the present study to develop a competitive extended release tablets of Metformin Hydrochloride by using the hydrophobic (EC) and hydrophilic polymer (HPMC) alone/ in combination have been used as coating and matrix material in order to get the required release and their effect on release pattern. [5-9]

MATERIALS AND METHODS

Metformin HCl was obtained from Alembic limited as a gift sample. Reference product Glumet XR (Cipla Ltd.) was purchased from local chemist. Methocel® K100M CR (HPMC) was collected as a gift sample from Colorcon Asia Pvt. Ltd. Avicel PH 101 (microcrystalline cellulose) was collected as a gift sample from FMC Biopolymer. Magnesium stearate was purchased from Signet. Potassium dihydrogan ortho phosphate and sodium hydroxide were obtained as gift samples from Merck Ltd. All other chemicals and reagents used were of analytical grades.

Preparation of hydrophilic matrix tablets

Extended release tablets were formulated by wet granulation matrix tablet technology using hydrophilic polymer, Hypromellose (Methocel® K100M CR). Trials were taken with different concentrations of Hypromellose and tablet weight as shown in table 1. Accurately weighed quantities of Metformin Hydrochloride, Hypromellose, Lactose monohydrate, Povidone K-30 and Microcrystalline cellulose were dispensed as per formulation table 1 in clean dispensing booth and sifted through 40# sieve. The sifted material was mixed uniformly in polybag for 10 minutes and granulated with the hydroalcoholic binder solution (PVP K 30) by adding drop wise with continuous mixing to get optimum granulation. The wet mass was dried in tray drier, sifted through 20# sieve and weighed. The blend was lubricated with magnesium stearate dispensed according to % yield and sifted through 60# sieve. The blend was properly mixed in polybag and compressed on 8-station compression machine using specified punches according to table 1for 500mg strength of tablets.

Table 1 Composition of Metformin HCl extended release tablets

Ingredients	F1	F2	F3	F4	F5
Metformin HCl	500	500	500	500	500
Lactose monohydrate	120	80	40	100	25
Hypromellose	80	120	160	250	375
Microcrystalline cellulose	NA	NA	NA	100	50
Povidone K30	50	50	50	30	30
Water:IPA(1:1)	q.s	q.s	q.s	q.s	q.s
Mg. Stearate	10	10	10	20	20
Tablet Weight (mg)	760	760	760	1000	1000
Punch size	17.15×7.15 mm*	17.15×7.15 mm*	17.15×7.15 mm	19×8 mm#	19×8 mm#

* Oval Shaped, # capsule shaped

Functional coating using hydrophobic polymer

Functional coating of formulation F3 was done with hydrophobic polymer Ethyl cellulose (Ethocel® 7CPS) and PEG 4000-F as plasticizer (60:40 %w/w) to meet the target profile of reference product as shown in table 2. Coating solution was prepared using Isopropyl alcohol: Dichloromethane: Water (30:65:5). Coating was done in conventional coating pan till weight gained up to 3%, 5% and 7% for F3a, F3b and F3c batches respectively.

Table 2 Coating composition for Formulation F3

Coating Ingredients	F3a (3%)	F3b (5%)	F3c (7%)
Ethyl cellulose (Ethocel® 7cpS)*	60	60	60
PEG 4000F*	40	40	40
IPA:DCM:Water	35:65:5	35:65:5	35:65:5

*Composition of each ingredient is given in percentage

Evaluationof blends

The formulated powder blends were evaluated for angle of repose, bulk density, tapped density, percentage compressibility index and % loss on drying. [10-12]

Evaluation of Tablets

The compressed tablets (formulations F1 to F5) and reference standard were tested for hardness, thickness, percentage friability and weight variation test. Hardness of tablets was tested using Dr. Schleuniger hardness tester (8M). The thickness of the tablets was measured by digital vernier caliper (Digimatic). Friability of the tablets was determined in a Roche friabilator (Electrolab). Weight variation test was performed according to the official method (Indian Pharmacopoeia, 1996).

Table 3 Evaluation of blends F1 to F5

Parameter	F1	F2	F3	F4	F5
Bulk Density	0.45	0.54	0.49	0.43	0.45
Tapped Density	0.52	0.63	0.59	0.55	0.55
Compressibility index	13.46	14.28	16.95	21.81	22.22
Hausner's ratio	1.15	1.16	1.2	1.29	1.22
Loss on drying (%w/w)	2.68	2.37	2.36	2.12	2.67
Angle of repose (θ)	33.69	29.74	32.41	33.69	36.52

Assay of tablet

Three tablets were taken from each batch. Every tablet was crushed individually, dissolved in 1000 ml of phosphate buffer pH 6.8 and sonicated for 15 minutes. 5ml of solution was taken from each sample and diluted up to 25ml in 25ml volumetric flask. From this solution 1 ml of solution was withdrawn and diluted up to 10ml in 10ml volumetric flask. Absorbance of the solution was measured at 232 nm. The concentration of Metformin Hydrochloride was calculated using slope of calibration curve and % assay was calculated using the following equation:

$$\% \text{ Assay} = \frac{\text{Conc. (µg/ml)} \times \text{Media Vol.} \times 100}{1000 \times \text{Dilution Factor} \times \text{Label claim}}$$

***In-vitro* drug release study**

In-vitro drug release studies of extended release tablets were performed in automatic USP dissolution apparatus 1, basket type (Electrolab, Mumbai, India) at the speed of 100 rpm. Dissolution tester USP (Elactrolab TDT-08L) was connected with Electrolab peristaltic pump, for automatic sample withdrawal and replacement of media, and Elactrolab fractional collector, for collection of sample. Phosphate buffer pH 6.8 was used as a dissolution media. The bowls of the dissolution tester was filled with 1000ml of phosphate buffer pH 6.8 and allows to attaining a temperature of 37±0.5ºc. The reservoir for the replacement of the media was also filled with phosphate buffer. Apparatus was started when temperature achieved to 37±0.5ºc and the tablet was placed to the bottom of the basket. The protocol of the dissolution apparatus was set for automatic 10ml sample withdrawal and replacement of fresh media at predetermined time interval i.e. 1hr, 2hr, 4hr, 6hr, 8hr, 10hr, 12 hr, 16hr, 20hr and 24hr. Thesamples withdrawn were filtered through a 0.45 µ membrane filter(Nunc, New Delhi, India) and the drug content in each sample wasanalyzed by UV spectrophotometer after suitable dilution(Shimadzu UV-1700) at 232 nm.[13] Drug dissolved at specifiedtime periods was plotted as percentage cumulative release versis time (hours) curve.

Kinetics of Drug Release

In order to investigate the mechanism of drug release from extended release tablets of Metformin HCl, the release rate obtained from dissolution studies were fitted to various kinetic equationsas shown for reference product[14-16].The kinetics models used were a,

Zero order equation($Q_t = Q_0 - K_0t$), First order equation ($\ln Q_t = \ln Q_0 - K_t$), Higuchi's equation($Qt = K_h t^{1/2}$)

The regression coefficient (R^2) value obtained from the log %ARR (Amount Remaining to bereleased) versis time was examined to find out the release mechanism.

Swelling index

Tablet of each trial was weighed initially and kept on cover slip in the petri-plate filled with 6.8 pH phosphate buffer. After specific time intervals weight gained by

tabletwas measured up to 24 hours till the weight remains constant. The % weight gain by the tablet was calculated by the formula,

Where, S.I. = Swelling index
Wt = Weight of tablet at time t
Wo = Weight of tablet at different time interval.

Stability study

Stability study was carried out for the optimized formulation for following condition and time period as per ICH guidelines [17]: $25^0C \pm 2^0C$ (60% ± 5% RH), $30^0C \pm 2^0C$ (65% ± 5% RH) and $40^0C \pm 2^0C$ (75% ± 5% RH). Six tablets were individually packed in Alu-Alu bag, sealed properly and put at above specified condition in incubator for 3 months. Tablets placed for stress testing i.e, $40^0C \pm 2^0C$ (75% ± 5% RH) were evaluated for in-vitro drug release, and content determination after one, two and three month. Tablets placed for long term testing i.e, $25^0C \pm 2^0C$ (60% ± 5% RH) and intermediate testing i.e, $30^0C \pm 2^0C$ (65% ± 5% RH) were evaluated for same parameters after three months.

Table 4 Evaluation of tablets of formulations F1 to F5, F3a, F3b and F3c

Batch No.	Weight (mg)*	Hardness (Kp)*	Thickness (mm)*	Friability (%)*	% Assay**
F1	749.88 (±2.55)	13.50 (±0.82)	6.73 (±0.019)	0.210	97.85 (±0.37)
F2	750.08 (±1.36)	13.48 (±0.36)	6.76 (±0.03)	0.263	98.22 (±0.34)
F3	750.24 (±2.09)	11.78 (±0.52)	6.71 (±0.009)	0.268	99.22 (±0.46)
F4	1003.24 (±2.84)	15.36 (±0.46)	6.79 (±0.054)	0.324	98.81 (±0.41)
F5	1002.24 (±2.47)	15.04 (±0.70)	6.79 (±0.038)	0.369	98.85 (±0.33)
F3a (3%)	774.88 (±1.12)	15.3 (±0.87)	6.71 (±0.13)	0.056	99.32 (±0.34)
F3b (5%)	789.93 (±1.58)	19.7 (±0.65)	6.83 (±0.20)	0.047	99.12 (±0.46)
F3c (7%)	804.98 (±1.86)	21.9 (±0.54)	6.97 (±0.17)	0.035	98.83 (±0.41)

*Each reading is an average of five determinations. (Avg.± S.D)
**Each reading is an average of three determinations. (Avg.± S.D)

RESULTS AND DISCUSSION

Powder blends were evaluated for angle of repose, bulk density, tapped density, percentage compressibility index and % loss on drying. The results are shown in table 3.Bulk density was found in the range of 0.450-0.540 gm/cm^3 and the tapped density between 0.520-0.630 gm/cm^3. All powder blends except formulation F4 with Hausner's ratio (<1.25) indicated better flow properties. The compressibility index for formulations F1, F2 and F3 was found between 13.46 and 16.95, which indicated good flowability. While formulations F4 and F5 showed poor flowability due to compressibility indexes 21.81 and 22.22 respectively. For all formulations angle of repose was found in the range of 29.74-36.52 (<40°), indicating good flow properties.

In order to optimise the formulation extended release tablets of Metformin HCl were prepared by two strategies: Matrix tablet using hydrophilic polymer, Combination of matrix and reservoir by hydrophilic polymer core and hydrophobic coating.

Prepared tablets were evaluated for weight variation, thickness and hardness and % assay which are shown in table 4. Due to good flowability of blends, formulated tablets were of uniform weight, with acceptable weight variations as per pharmacopoeial specifications. Thickness of formulations F1, F2 and F3 was found between 6.71mm to 6.76 mm. The average thickness of these formulations was found to be 6.72 mm with deviation ±0.019mm. While average thickness of formulations F4 and F5 was 6.79 mm with deviation ±0.046 mm. The hardness of the formulations F1, F2, and F3 was found to be 11.78 to 13.50 Kp, and for the formulations F4 and F5 it was found to be 15.36Kp to 15.04Kp. All formulations showed less than1% (w/w) friability which was within the prescribed limits. [18]

The results of the swelling index which are shown in **Figure 2**, reveals that the hydration rate and water uptake of the formulation increase with increasing concentration of the polymer combination. The graph of swelling index verses time (Hr.) is shown in **Figure 2**. Swelling index of the formulation F1 was decreased after 20 Hr. due to lower polymer concentration. Hydration rate and water uptake of the formulation F2, F3, F4 and F5 was almost similar indicates there was no major effect on swelling index after 10.66% polymer concentration.

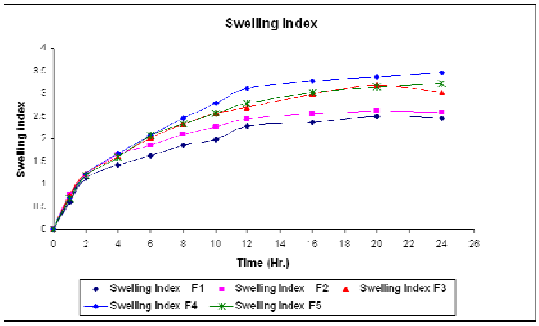

Figure 2 Swelling index verses Time (Hr.) of formulations F1 to F5

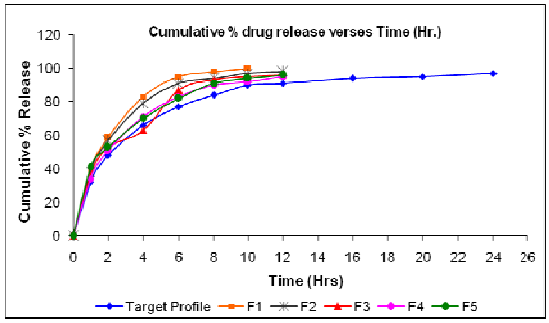

Figure 3 Comparative dissolution profiles of formulations F1 to F5 with Glumet XR

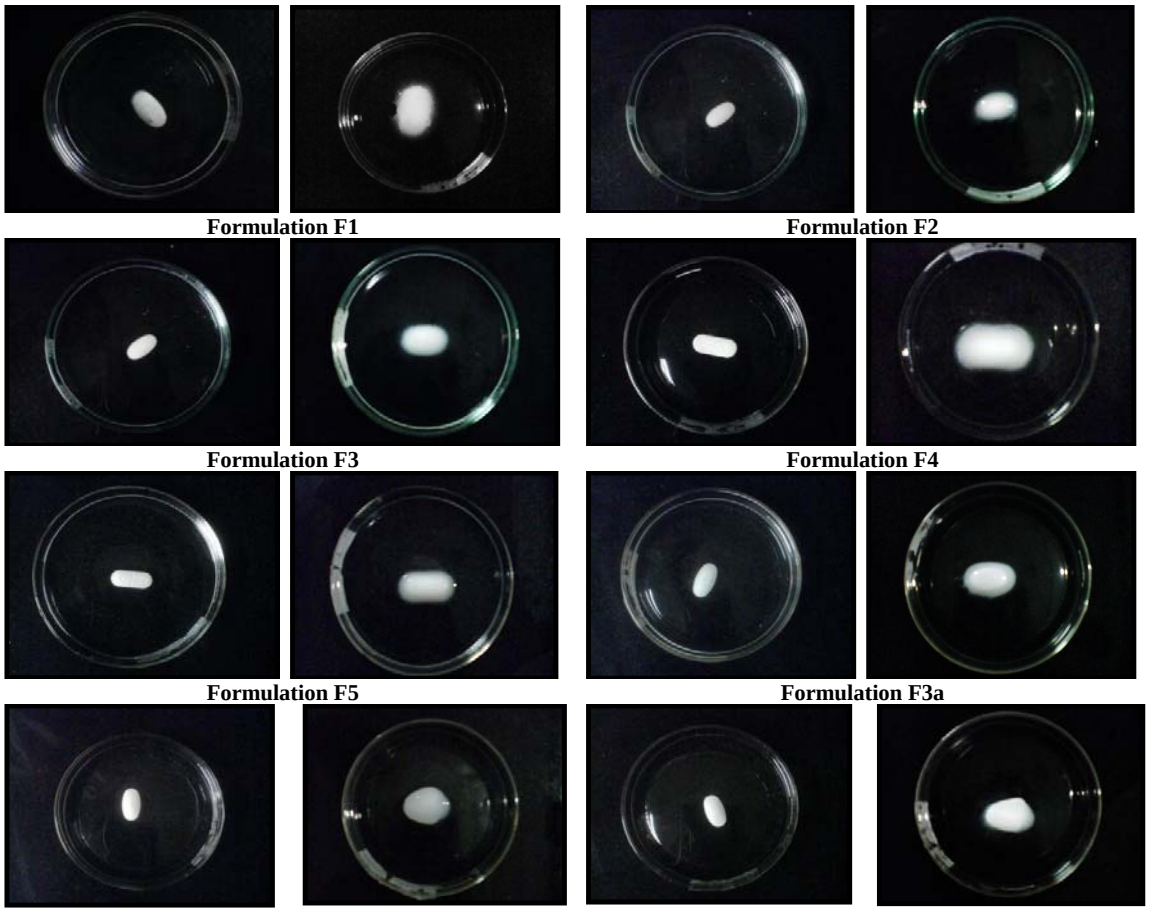

Figure 1 Tablets before and after water uptake (F1 to F5, F3a, F3b and F3c)

In-vitro drug release depends on several factors, such as the manufacturing process, the type of excipients and theamount of drug. The results of *In-vitro* dissolution studies of formulations F1 to F5 are shown in **Figure 3.** Dissolution profiles for Cumulative percentage drug release verses time (Hr.) are shown in **Figure 3**.

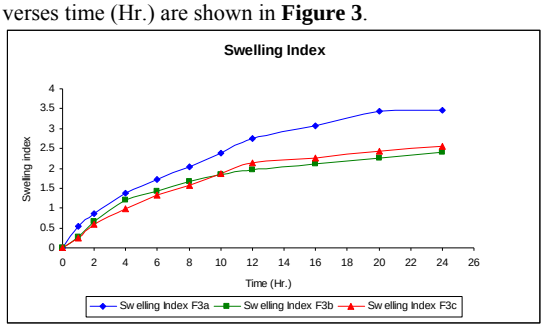

Figure 4 Swelling index of batches F3a, F3b, F3c

The cumulative % drug release of reference product (Glumet XR) and formulations were compared by similarity factor (f2) and difference factor (f1) values.From the results, it was revealed that *In-vitro* drug release of F1, F2 and F3 formulations;containing increasing amount of rate controlling polymer, i.e. hypromellose, (80, 120 and 160mg) per tablet were faster than the reference product. Hence, the two trials were taken at 1000 mg tablet weight using 250 and 375 mg hypromellose, and by adding water insoluble excipient, i.e. microcrystalline cellulose. The dissolution profile of these two formulations was also faster than the reference product.Cumulative percentage drug release, which was obtained from *in-vitro* dissolution study of the formulations F1 and F2, was not satisfactory. And the values of f2 and f1, as indicated in individual dissolution profiles was also not obtained upto the desired extent. Initial bursting effect and fast dissolution profile was observed in formulations F1 and F2 due to lower concentration of polymer.

While, the formulation F3 showed satisfactory results of cumulative percentage drug release. The values of f2 = 59.64; f1 = 8.40 revealed that, the curves of reference product and formulation F3 can be considered similar. But the initial burst effect was still observed, which was less as compared to formulations F1 and F2.

Cumulative percentage drug release and values of f2 and f1 for the formulations F4 and F5 was not found to be satisfactory. They showed faster release profile and both formulations were not considered due to higher weight of tablet as compared to F3.

So, the attempt was taken for functional coating (Hydrophobic coating) on formulation F3 for the prevention of initial burst effect and to prolong the drug release for extended period of time.Functional coating (modified

release film coating) was applied on the formulation F3 using Ethyl cellulose (as hydrophobic film former) and PEG 4000-F (as plasticizer). 3% (F3a), 5% (F3b) and 7% (F3c) coating was applied by calculating target weight based on average weight of core tablet. The tablets were withdrawn at different interval as 3%, 5% and 7% coating was achieved.

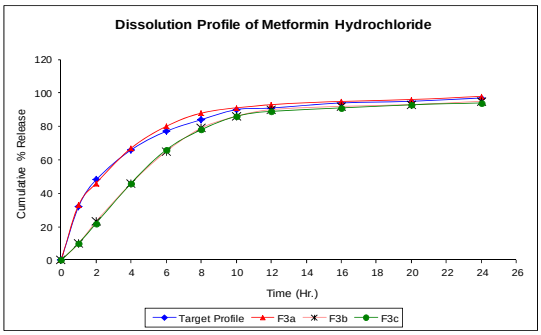

Figure 5 Comparative dissolution profiles of batches F3a, F3b, F3c with Glumet XR

Thickness of tablets F3a, F3b and F3c was found between 6.71 mm to 6.97 mm. The average thickness of these formulations was found to be 6.84 mm with deviation ±0.017mm.The hardness of the formulations F3a, F3b, and F3c was found to be 15.3, 19.7 and 21.9 respectively as shown in table 4. Here also, all formulations showed less than1% (w/w) friability which was within the prescribed limits. [18]

The results of the swelling index as shown in **Figure 4** reveal that the hydration rate and water uptake of the F3a formulation decrease as compared to core tablets (F3). Swelling index of the F3b and F3c formulation was decreased more as compared to core tablets, which is shown in **Figure 4**. Hydration rate and water uptake of the F3b and F3c formulations was almost similar indicates that, there was no major effect of coating on swelling index, after 3% coating.

Cumulative percentage drug release, which was obtained from *in-vitro* dissolution study of the F3a formulation showed satisfactory results, and the values of f2 = 80.29; f1 = 2.87 indicated that, the curves of reference product and formulation F3a can be considered almost similar, which is shown in Figure5. And the initial burst effect was also been suppressed. The drug release data from the batches F3a, F3b and F3c are shown in Figure 5. Cumulative % drug release profile for the formulations F3b and F3c was suppressed to higher extent and were similar with each other. And they did not showed satisfactory results of the curve values, f2 and f1 with reference product.

The regression coefficient (R^2) values obtained from the log %ARR (Amount Remaining to Release) verses time were0.6295, 0.9396 and 0.8673 for zero order, first order and Higuchi model respectively. The value nearer to one indicates first order release for formulation F3a. Results of stability study carried out on formulation F3a for three months indicated that, there was no any significant change in drug release of the tablet. And % assay results were found within specifications. Hence, the optimized formulation was stable.

CONCLUSION

In the present research work extended release tablets of Metformin Hydrochloride were prepared by different strategies: Matrix tablet using hydrophilic polymer, Combination of matrix and reservoir by hydrophilic polymer core and hydrophobic coating

So, the attempt was taken for functional coating of formulation F3 using hydrophobic polymer i.e. Ethyl cellulose (Ethocel® 7cpS) and 3%, 5% and 7% coating was applied for the batches F3a, F3b and F3c respectively. The results of these trials revealed that, the F3a (3% coated) batch showed satisfactory results for f2 and f1 values. And the dissolution profile was almost similar with that of reference product. Other trials F3b and F3c did not shown satisfactory results. The formulation F3a was kept for stability study where, results of % assay and in vitro dissolution study of stability batch F3a were found to be satisfactory.

Hence, from above results obtained, it can be concluded that the formulation F3a (3% coated) showed better extended release profile of the drug, as compared with reference product and was also stable after stability study.

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