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DEVELOPMENT AND IN-VITRO CHARACTERIZATION OF TIROPRAMIDE TABLETS HAVING IMMEDIATE- AND EXTENDED RELEASE LAYERS

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ABSTRACT

Purpose: The objective of this study was to explore the feasibility of developing of Tiropramide, bilayer tablet using an immediate- and extended-release formulation. **Method:** After rheological performance of drug-excipients mixture, Tiropramide HCl bilayer tablets were prepared by wet granulation method. FTIR analysis was performed to elucidate the compatibility behavior of drug and excipients. Effect of these varying concentrations of Ethyl Cellulose (EC) and Hydroxy Propyl Methyl Cellulose (HPMC) were observed on the sustained release pattern of the matrices. Dissolution was performed by using 0.1N HCl and phosphate buffer pH 7.2 as medium at 37.0 ±0.5 ºC, while the stirring speed was set at 50RPM. The bilayer tablets were stored under conditions 40±2ºC temperature and 75±5% humidity for stability testing. **Results:** It was observed that as the quantity of polymers (HPMC or EC) increases the sustained release effect also increases. It was obvious from these models that drug release form bilayer tablets followed the zero order model and Higuchi square root model and the drug release mechanism was diffusion and erosion. The polymers-drug combination was compatible in bilayer tablets before and during stability testing. **Conclusion:** Bilayer tablet of Tiropramide can be developed successfully in which one layer provides immediate release while the other prolongs the drug release.

Keywords: Bilayer tablet, Tiropramide HCl, Floating, Sustained release, HPMC, Ethyl Cellulose

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INTRODUCTION

For decades, tablet dosage form is most useful technique for distribution of drugs in the body. Variation in concentration and distribution of drug are common in conventional dosage forms **[1]**. Sustained release tablets are better than other techniques in constant distribution of drug and decrease in frequency **[2**]. Different procedures are used for the formulation development and characterization of tablet dosage form. Schemes including mucoadhesive, bioadhesive expanding, swelling, floating and devices used in emptying **[3, 4]**. The interest is increasing to build the bilayer tablet i.e. one component is immediate layer and other is sustained release.

Today's concern is not just to produce elegant and accurate dosage forms but also to ensure that optimum amount of drug reaches the target site at an optimal rate and its concentration is maintained for the entire duration of therapy. Though pharmaceutical industries are now looking for alternative way of administration of drugs **[5]**. To keep the plasma concentration of drug above minimum effective concentration level, multiple administrations are required to accomplish it. Therefore, it necessitates in developing suitable dosage form with a steady state release characteristic for an extended period. There are many extended release pharmaceutical dosage forms **[**6**]**. There is no hindrance for large scale production of bi-layered tablets from industrial stand point. Besides this, preparation is cost effective when compared with other controlled release dosage form.

To overcome high frequency conventional oral tablets, there is increased interest in developing controlled drug delivery. Bilayer tablet is successful new era for development of controlled release formulation. Bilayer tablet technology, an excellent improved technique for providing combine release pattern of drug i.e. immediate release and sustained release. In this system two incompatible drugs combined together in single dosage form. There are different approaches available for bilayer tablet technique. Biphasic system formulated with drug having analgesics, antipyretics, antiallergenic,

coronary vasodilators, antihypertensive and antihistaminic activity.

The objective of study was to control the delivery rate of tiropramide HCl from the bilayer tablet and to reduce the frequency of the dose during the therapy. The immediate layer will provide loading dose for achieving therapeutic level whereas the sustained release layer will continuously maintain the plasma level over an extended period of time.

METHODOLOGY

Materials

Tiropramide Hydrochloride was gifted by (Popular Chemical Works Pakistan). Hydroxy methyl cellulose (Methocil K15) were supplied by (Rawlon Chemicals). Ethyl cellulose (Methocil E5), Avicel pH 102, Lactose, PVP k30, Magnesium Stearate, Talcum and Rectified Spirit were obtained as gift sample from BJ Pharma Pakistan.

Preparation of Granules and Bilayer Tablet

Tiropramide, HPMC, Ethyl cellulose, Methocil k15, Avicel and lactose sifted through sieve no.30 according to the formulation F1 to F8. The sifted materials were mixed in a polythene bag. The mixed materials were granulated using granulating solution of PVK30 to get a damp mass, pass through sieve no.6. These granules were air dried for 15 minutes and finally dried in hot oven at 40ºC – 45ºC till load was >2% and passed through sieve no. 12. The obtained granules were mixed with magnesium stearate and talcum as lubricant. Firstly the contents of sustained release layer were compressed at low pressure using 9mm die-punch and then immediate release layer were compressed on it.

Characterization of IR/SR Granules

The loss on drying of compression mixtures was performed on approximately 10 g samples using a Mettler HR73 halogen dryer (Mettler Toledo, Greifensee, Switzerland). The drying method lasted 5 minutes at 105 °C. One average sample was used for each technological procedure **[7]**.

According to the (USP) method-I assumed to determine the bulk density by using the measuring cylinder. According to this, firstly granules were passed through sieve #20. After that, granules were transferred into a dry glass cylinder without compressing and volume occupied by the granules was measured (USP-29).

Also termed as tapped density and was describe by the USP process –I for tapped density. In this process, granules of each batch of matrix tablet was pre-sieved and presented into the dry cylinder. After defining the initial volume, the cylinder was manually tapped (almost 100 times tapped) till no more size change occurred. The final volume was check and tapped density was measured.

In this process, Powder granules blend was passing through a glass funnel fixed with a position at stable height. Under the force of gravity powder /granules were drawn **[8]**. Graduated scale is used to measure the height and diameter of pile. High values of angle of repose specify that powder granules is difficult to flow and cohesive in nature (USP-2009)

A method accepted by Carr, to measure the degree of flow properties of granules using bulk densities called Carr's index or compressibility index. It measures the compressing tendency of Powder granules and is interrelated to the inter-particle interfaces. The assessment of densities classifies the Powder granules based on flow properties **[9]**. Ratio between tapped density to the bulk density called Hausner's ratio. This ratio is correlated to inter-particle friction which disturbs the flow characteristics of Powder /granules. Normally values less than 1.2 indicate that powder/Granules is free flowing, or having less inter-particle friction and values greater than 1.6 indicate powder is cohesive in nature **[10].**

Table 1: Formulations of IR and SR layers.

Ingredients	IR layer	SR layer							
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Tiropramide HCl	100	100	100	100	100	100	100	100	100
Starch	23	-	-	-	-	-	-	-	-
CMC Sodium	20	-	-	-	-	-	-	-	-
Rectified Spirit	57	-	-	-	-	-	-	-	-
Purified Water	0.01	-	-	-	-	-	-	-	-
Aerosil	4	-	-	-	-	-	-	-	-
PVP k-30	5	16	16	15	-	-	-	16	16
Magnesium Stearate	4	3.4	3.4	3.4	3.0	3.0	3.0	3.4	3.4
Methocil K15	-	70	109	122	-	-	-	-	-
Ethyl Cellulose	-	-	-	-	200	220	240	-	-
Methocil E5	-	-	-	-	-	-	-	90	-
Avicel	-	-	-	-	-	-	-	-	90
Lactose	-	51	12	-	-	-	-	31	31
Talcum	2	5	5	5	2	2	2	5	5

Characterization of Tablets

Weight Variation

Twenty tablets were randomly selected and from each batch and average weight were calculated. Then individual tablet were weighted and individual weight was compared with an average weight.

Friability

Twenty tablets were weighed and placed into the friabilator and operated at 25rpm for four minutes. At the completion of revolution the tablets were reweighed. The tablets should nor loss more than 1%. Friability was measured by using the following formula.

$$Friability = \frac{Weight\ Loss}{Initial\ Weight} * 100$$

Hardness Test

Hardness was checked by hardness tester (Pharmatech). Randomly tablets were taken, hardness was checked **[11]**. Hardness defines as a capability of a tablet to withstand during handling, and mechanical shocks. To measure hardness digital hardness tester was used. Randomly select 10 tablets from each batch to check hardness and also calculate mean and standard deviation **[12].**

Compatibility Studies

IR Spectroscopy was performed to check the possible incompatibilities structural changes between the polymer-polymer, drug polymer and excipients, formulations. FTIR analyzer was cleaned properly using methanol to remove the spots. Samples of drug polymer, Pure drug, polymer was placed to the sample loading edge and scanned in mid IR, ranged 4000 to 400cm^{-1} (λ=221nm) **[13].**

In Vitro Drug Release Study

In-vitro drug release studies were carried out using USP type II dissolution testing apparatus in 900 ml of 0.1N HCl solution for first two hours and replaced with phosphate buffer pH 7.2 from 3rd to the 8th hour with speed of 50 rpm. For both media the temperature was maintained at 37 ^{o}C ± 0.5 ^{o}C. The sample was collected as per selected time (0.5, 1, 2, 3, 4, 5, 6, 7, 8 hrs) intervals with replacement of equal volume of dissolution media. The absorbance of collected samples was measured spectrophotometrically at the wavelength of 225 nm **[14]**.

Kinetic Release of Modeling Drug

Mechanism and order of drug release from developed formulations were evaluated by applying in-vitro release data in different kinetic models including zero order, first order, Higuchi model, Kormeyer-Peppas models (Power law) and Weibull model **[15].**

Stability Study

The bilayer tablets were packed in suitable packaging and stored under conditions 40±2 ^{o}C temperature and 75±5 % humidity for a period as prescribed by ICH guidelines for accelerated studies. The tablets were withdrawn after a period of 1, 3 and 6 months and analyzed for physical characterization (visual defects, hardness, friability) dissolution and drug content **[16]**.

Table 2: Pre-compression values of granules.

Formulation	Loss on Drying (%)	Bulk Density (Kg/m^3)	Tapped Density (Kg/m^3)	Angle of Repose	Compressibility Index	Hausner's Ratio
F-1	2.2	0.384	0.453	29	15.23	1.179
F-2	2.1	0.451	0.530	30	15.09	1.175
F-3	2.2	0.432	0.505	30	14.45	1.168
F-4	2.3	0.418	0.497	31	15.89	1.188
F-5	2.5	0.376	0.445	29	15.50	1.183
F-6	2.4	0.382	0.450	31	15.11	1.178
F-7	2.3	0.422	0.502	29	15.93	1.189
F-8	2.4	0.426	0.511	30	16.63	1.199

Figure 1: A bilayer tablet of tiropramide.

Table 3: Physical and chemical testing of all formulations (F1-F8).

Tests	Specifications	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F8
Average weight (mg)	Avg.wt mg ±5%	245.5mg +158mg	245.4mg +158mg	245.4mg +158mg	305mg +158mg	325mg +158mg	345mg +158mg	245.5mg +158mg	245.5mg +158mg
Weight Variation	Avgwt mg±5%	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Thickness (mm)	5.0– 6 mm	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Hardness (kg/cm2)	NLT 4 kg/cm^2	5.7	5.9	6.3	5.8	6.2	6.4	6.2	5.9
Friability (%w/w)	NMT 1%	0.71	0.63	0.60	0.81	0.74	0.71	0.51	0.44
Assay each tablet contains 200 mg tiropramide	90-110 % of the stated amount	100.2	99.3	100.2	101	99.4	99.9	100.5	99.8

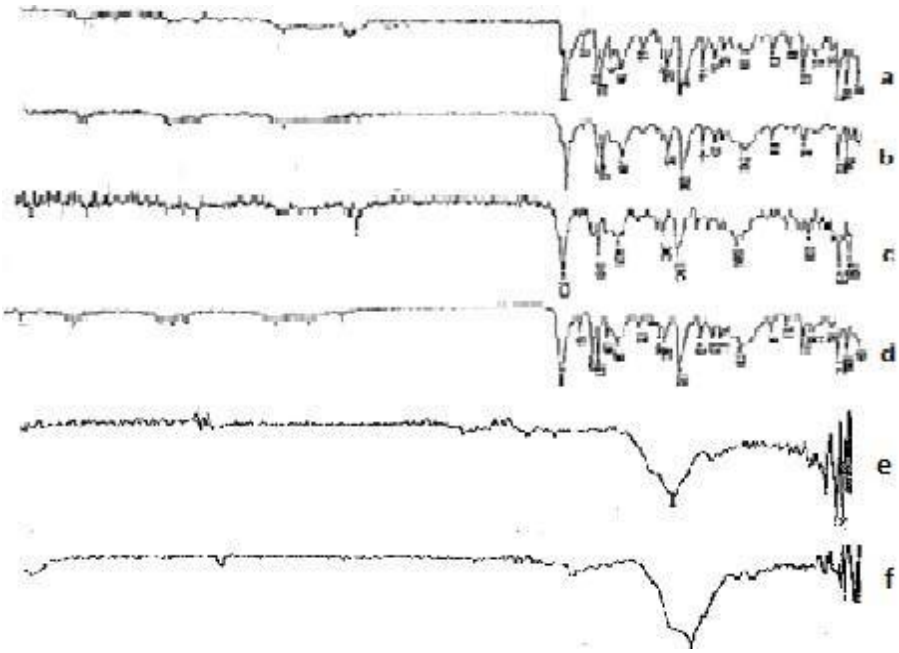

Figure 2: Fourier transform infrared spectrum of (a) tiropramide HCl (b) F3 formulation (c) F6 formulation (d) immediate layer of tablet (e) HPMC k15 (f) ethyl cellulose.

RESULTS AND DISCUSSION

Pre-Compression Testing (Grain Characterization).

Angle of Repose

The angle of repose of pure drug was more than 40±2, Carr's index was also more than 20. Therefore pure drug have poor flow properties and compressibility. Hence the different problems i.e. weight variation, low hardness; capping and sticking of the tablet were found. Then these problems were solved by wet granulation and adjustment of binders, lubricants and LOD in the grains just improving the angle of repose 30±1.5, and Carr's index 15±1**.**

Density

The bulk densities for the granules of various formulations ranged between 0.376 -0.451 kg/m^3 and tap density 0.445 – 0.530 kg/m^3. This value of bulk density indicates of good packing character **[17]**. The bulk density and tap density was used to calculate the percent compressibility of the granules. The Carr's index was observed between 14.45 – 16.63,

indicating good compressibility of the granules (Table 2).

Hausner's Ratio and Carr's Index

Initially, Hausner's ratio was more than 1.20. It mean existing inter-particulate friction and therefore little free flow of grains **[18]**. Hausner's ratio values 1.168-1.199 was achieved and hence good flow property was attained by lubrication, making the suitable size of the grains and suitable loss on drying.

Post Compression Testing Evaluation

Hardness

Hardness depends upon the quantity of binder, geometric structure and surface wettability. The hardness was found to be in the range of 5.7 – 6.4 kg/cm^2. This ensures good mechanical strength.

Friability

Friability of the all formulations F1-F8 was found in the range of 0.44 – 0.71% which was within specified limits. Tablets with friability less than 1% of their weight are acceptable. Crushing strength and moisture content vary the friability (table 3).

Physical Appearance

It was pink layer at one side and other white layer. No black particles, capping or sticking present.

FTIR Spectroscopy

Absence of any interaction between API and all other components employed in the formulation was confirmed by FTIR Spectroscopic studies. Tiropramide HCl spectrum was presented in Figure 2. The pure drug exhibited major peak at 1634 cm^{-1} due to stretching of O-H group (Hydrogen bonding) and 2930 cm^{-1} for C-H stretching of OCH_3. Peaks at 2862 cm^{-1} and 2514 cm^{-1} are assigned for –C-H stretching of $–CH_2$ and CH_3 groups while absorption band at 1607 cm^{-1} and 1578 cm^{-1} is due to C=C aromatic ring stretching. The peak at 1288 cm^{-1} and 1315 cm^{-1} for –C-H bending of symmetrical and a symmetric of $-CH_2$ and $–CH_3$ group. The peak 1242 cm^{-1} and 1045 cm^{-1} may be due to –C-O-C group. Substituted benzene ring showed peak at 780 cm^{-1} and 702 cm^{-1} may be due to O-H bonding. Similar peaks due to hydrogen bonding at 3305 cm^{-1}, -C-H stretching of $-OCH_3$ at 2924 cm^{-1}, C-H stretching of $–CH_2$–CH groups at 2510 cm^{-1}, 2850 cm^{-1}, C=C ring stretching at 1604 cm^{-1}, 1570 cm^{-1}, -C-O-C group and substituted benzene ring peaks 1042 cm^{-1} and 780 cm^{-1} was reported.

Physical mixture and all the formulations contain characteristics bands of drug demonstrating no considerable variation in given peaks which depicts the absence of any interaction among drug, polymer and other ingredients. There is no change in the major peaks of Tiropramide HCl and all other formulation i.e. F1 – F8. So, there is no incompatibility between excipients and API. So, all the formulations are stable **[19].**

There is no change in the major peaks of Tiropramide HCl in all formulation and no new bands were observed. So there is no incompatibility or chemical interaction between excipients and API. So, pure drug is stable in all the formulations F1 – F8 **[19**]. Physically of the drug and polymers was responsible for sustained release features.

Dissolution Profile of Different Formulations

The release profile of tiropramide hydrochloride from the prepared formulations was analyzed by plotting the cumulative percent drug released vs time as shown in Figure 3. Simple visual observation of the plot shows an initial burst effect from F1 – F6 the formulations over 40 % of tiropramide is released within 30 minutes of the dissolution study. This initial high amount of tiropramide hydrochloride release can be attributed with immediate release layer of the formulation.

The immediate layer when it comes in contact with the dissolution medium and hence it facilitates the tablet to erode. In Immediate layer the Starch and CMC facilitate the dissolution. The release required 100% which was achieved within 30 minutes. Immediate layer disintegrated with simultaneous imbibition of dissolution medium by tablet.

HPMC k15 and Ethyl cellulose had been used as polymers for release retardant in sustained release dosage forms. EC reduce the drug release due to a reduction in the penetration of the solvent molecules into the system because of the hydrophobic nature of ethyl cellulose present on the surface of the tablet; the rate of release is controlled by the penetration of matrix structure. As the proportion of ethyl cellulose increase, the release process of the drug decrease. In F4 formulation the standard release profile is not achieved. As the amount of ethyl cellulose was increased the required result was obtained. In F6 formulation required entrapment of drug is achieved. In HPMC the gel formation was observed and in F3 formulation in which 122 mg HPMC per tablet was used and best release profile was taken. The less amount of HPMC per tablet was used as compared to ethyl cellulose to take the standard results.

Kinetic Modelling of Release

Rate constants of each model are given in table 4**.** This model illustrates that discharge of drug from system follows Fick's law of diffusion and is dependent on square root of time. When the data were plotted according to zero-order kinetics the formulations showed correlation coefficient values R^2 between0.941 -0.982 for F1- F6 formulations **[20]**.

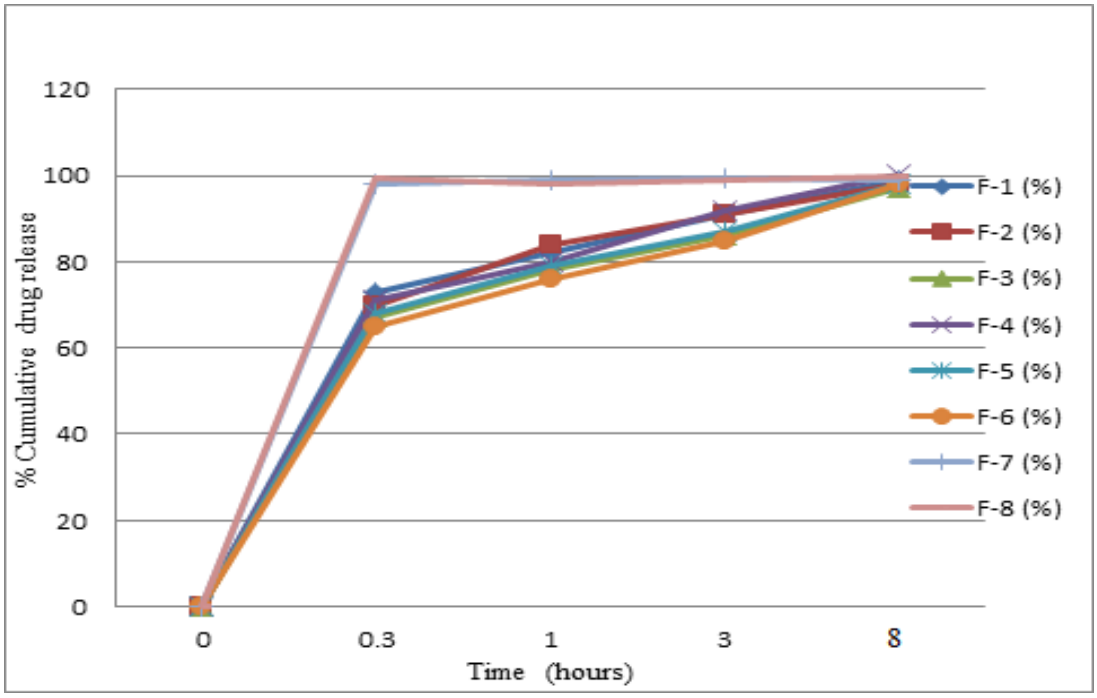

Figure 3: Drug release pattern of bilayer tablets of all formulations (F1 –F8).

Table 4: Kinetic modeling of all formulations (F1-F8).

Formulation	Zero- Order Model	First Order Model	Higuchi Kinetic Model	Korsmeyer – Peppas Model	Weibull Model
	R^2	R^2	R^2	R^2	R^2
F1	0.958	0.739	0.985	0.993	0.733
F2	0.941	0.733	0.986	0.998	0.687
F3	0.953	0.734	0.947	0.985	0.810
F4	0.956	0.804	0.965	0.998	0.743
F5	0.982	0.777	0.965	0.986	0.756
F6	0.964	0.783	0.998	0.975	0.831
F7	0979	0.801	0.978	0.981	0.785
F8	0.971	0.822	0.985	0.954	0.832

But when the data were plotted according to first order kinetic, the formulations F1 –F6 showed the correlation coefficient values 0.733 – 0.822. From the results it was found that only formulations F1- F6 follow the first order kinetics **[21]**. For determining the drug release mechanism, the in-vitro data were also subjected to Higuchi diffusion. The R^2, values of Higuchi diffusion plot were found to range between 0.965 – 0.998. For formulations F1 – F6 the values of all formulations were near to 1. So, it confirms the drug release by Higuchi diffusion mechanism. In Korsmeyer - Peppas model 'n' value of all formulations was above 0.5 concluding drug release by non-Fickian diffusion. Results of kinetic modeling showed Higuchi model was the best followed by the formulations.

Stability Study

The results were checked according to stability study schedule and all parameters critical and non-critical were found satisfactory for F3 and F6 formulations. The data for stability study reveals that no critical change in drug content and dissolutions rates were observed.

Table 5: Stability study of F3 and F6 formulations.

Test		Specification	1st month	3rdmonths	6th months
F3	Physical Inspection	Oblong Shape tablet with one layer white in color and other side pink color	Complies	Complies	Complies
	Dissolution (RPM 50) 0.5hr (0.1N HCl) 1st hr (0.1N HCl) 3rd hr (phosphate buffer pH 7.2) 8th hr (phosphate buffer pH 7.2)	After 0.5hr 1hr 3hrs 8hrs	 66% 76% 85% 98%	 64% 75% 83% 96%	 63% 74% 82% 96%
	Assay: Each bilayer tablet contains 200 mg tiropramide HCl	90 – 110% of stated amount	103.4%	102.0%	101.10%
F6	Physical Inspection	Oblong Shape tablet with one layer white in color and other side pink color	Complies	Complies	Complies
	Dissolution (RPM 50) 0.5 hr (0.1N HCl) 1st hr (0.1N HCl) 3rd hr (phosphate buffer pH 7.2) 8th hr (phosphate buffer pH 7.2)	After 0.5 hr 1 hr 3 hrs 8 hrs	 66% 77% 85% 98%	 65% 76% 84% 97%	 64% 74% 85% 96%
	Assay: Each bilayer tablet contains 200 mg tiropramide HCl	90 – 110% of stated amount	101%	99.4%	98.6.0%

CONCLUSION

It was concluded that bilayer tablet with immediate release layer and sustained release layer can be developed using polymer HPMC k15 and ethyl cellulose. These tablets have quick release because of immediate layer whereas sustained release is possible due to SR layer. Tiropramide tablets are stable for many months beside compatibility among formulation components.

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