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Qbd-Based Formulation Development And Evaluation Of Floating Tablet Of Tetrabenazine Drug

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ABSTRACT:

The present studies discuss about the quality by design (QbD)-based development and evaluation of chronomodulated release drug delivery system of Tetrabenzine for management of bacterial infection. Initially, target product profile was defined and critical quality attributes were earmarked. Risk assessment study was performed for identifying the critical material attributes. Oral route has been commonly adopted and the most convenient route for drug administration. It has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes. Gastroretensive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After the release of a drug, the residual system is emptied from the stomach. The floating bioadhesive tablet was a promising approach. The addition of gel-forming and mucoadhesive polymer like HPMC, xanthan gum, carbopol, and polyethylene oxide and gas generating sodium bicarbonate along with citric acid was essential to achieve in-vitro buoyancy desirable drug release and excellent bioadhesive strength. The formulation retained a longer period of time floated in 0.1N HCl and provided sustained release of the drug. Hence it may increase the therapeutic efficacy of the drug by increasing the bioavailability and patient compliance.

Key words: Floating tablet, Gastroretention, Sustain release

Introduction:

Orally-administered controlled-release drug delivery systems are associated with the shortcomings of relatively short residence times in the human stomach as well as highly variable gastrointestinal (GI) transit times. Thus, considerable intra-individual and inter-individual dierences in the bioavailability of drugs are observable. There are numerous drug substances which may benefit from prolonged and controlled GI passage times. As a solution to the problem, gastroretentive drug delivery systems (GRDDS), which feature an enhanced gastric residence time (GRT), were developed. Several gastric retention approaches, such as flotation, have been proposed and analyzed. Despite the extensive research performed in the field of GRDDS, the development, the production, and the evaluation of floating devices are still challenging. The aim of the thesis was to come up with a formulation strategy which facilitates the design of innovative floating drug delivery systems (FDDS). In the development of oral

controlled drug delivery system, one of the main challenges is to modify the GI transit time. Gastric emptying of pharma-ceuticals is highly variable and is dependent on the dosage form and the fasted state of the stomach.

Normal gastric residence times usually range between 5 min to 2 h. In the fasted state, the electrical activity in the stomach, the inter-digestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and hence, the transit of dosage forms. It is characterized by four phases: Phase I–Period of no contraction (40-60 min), phase II–Period of intermittent contractions (20-40 min), phase III–Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave (10-20 min) and phase IV Period of Transition between Phase III and Phase I (0-5 min), However, this approach is accompanied with several physiological difficulties such as the inability to restrain and locate the controlled drug delivery system within the desired region of the gastro-intestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, *i.e.*, stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose 2. This has led to the development of oral gastroretensive dosage forms. Gastroretention is essential for drugs that are absorbed from the stomach, drugs that are poorly soluble or degraded by the higher pH of the intestine, and drugs with absorption which can be modified by changes in gastric emptying time. Gastroretensive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bio-availability, reduces drug wastage, and improves solubility for drugs that are less soluble in a high pH environment. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Various Types of Gastroretentive Dosage Forms:

A. Floating drug delivery systems

a. Non-effervescent systems

i. Colloidal gel barrier system
ii. Microporous compartment system
iii. Alginate beads
iv. Hollow microspheres/ Microballoons

b. (Gas-generating) Effervescent systems

B. Expandable systems

C. Bio/Mucoadhesive systems

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D. High-density systems

A minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. The apparatus used for the measurement operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to the stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

F = Fbuoyancy - Fgravity

F= (Df - Ds) gv--- (1)

Where, F = Total vertical force, Df = fluid density, Ds =Object density, v=volume, g= acceleration due to gravity.

Applications of Floating Drug Delivery Systems:

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows:

A. Sustained Drug Delivery
B. Site-Specific Drug Delivery
C. Absorption Enhancement

MATERIALS AND METHODS:

Materials used: API from Hetero, Lactose monohydrate (Pharmatose 200M) from DMV Fonterra, Hydroxy Propyl Methyl Cellulose K15M (Methocel) from Dow chemicals, Carbomer 974P NF (Biolpol) from Infinitec, Xanthan gum 180 (Xanthrul) from C P Kelco, Polyethylene oxide N80 (Polyox) from Dow chemicals, Sodium bicarbonate from Merck, Citric acid anhydrous from Merck, Magnesium stearate from Ferro Industries, Aerosil 200 from Evonik.

Defining target product profile (TPP)

As per the QbD-based approach of drug product development, the target product profile (TPP) was defined encompassing the summary of quality characteristics of the drug product for accomplishing the desired chronomodulated drug delivery for attaining maximal therapeutic benefits against bacterial infection. These particularly included the biopharmaceutical parameters of the drug and target drug delivery system.

Preformulation studies

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Drug-excipients compatibility studies

The drug-excipients compatibility studies were carried out by preparing 1:1 physical mixture of the drug with individual excipients used for preparation of the time- dependent drug release systems Tetrabenzine. The physical mixtures were stored in airtight containers at 4°C (control), 25°C (room temperature) and 40°C/65% RH (accelerated condition) up to 1, 2, 3 and 4 weeks. After the specified time period, the drug- excipients mixtures were evaluated for different physical observations like color change, odor, and physical state of the drug. Both FT-IR and DSC studies were performed to identify the possibility of chemical interactions between drug and excipients, if any.

Development of spectrophotometric analytical method

A double beam UV-VIS spectrophotometer (UV 3000+, M/s Labindia, Mumbai, India) equipped with holographic grating in Czerny-Turner mounting, high intensity tungsten, halogen and deuterium lamps with automatic changeover, and high sensitivity matched pair silicon photodiode detector was employed for analysis of the drug. Spectrophotometric absorbance of the samples were measured using a 10 mm quartz cell with the spectral bandwidth fixed at 1 nm and data analysis was performed using UV-WIN software ver. 5.2.0. The value of absorbance, used to calculate the concentration of Tetrabenzine, was scanned in the range of 200 to 400 nm to observe the absorption maxima (ʎmax).

Preparation of sustained release layer

The sustained release granules of Tetrabenazine were prepared by dry blending of drug with sustained release polymer (i.e., HPMC K4M, K15M, K100M) and diluent (i.e., Prosolv-HD60) in a clean and dry polyethylene bag and subjected to blending for 15 minutes with the help of hand. The blend was then subjected to lubrication by adding Aerosil 200 and mixing for 10 minutes. Subsequently, magnesium stearate was added and mixing was continued for another 5 minutes.

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Table 1: Drug-excipient compatibility study data at different time intervals

Excipients	Drug	Vial with punctured rubber closure/cap at 25°C (room temperature)				Sealed vial kept at 40°C/65% RH			
		1 week	2 week	3 week	4 week	1 week	2 week	3 week	4 week
Eud-L100 D55	1:1	No change	No change	No change	No change	No change	No change	No change	No change
MCC-PH101	1:1	No change	No change	No change	No change	No change	No change	No change	No change
Mg. Stearate	1:1	No change	No change	No change	No change	No change	No change	No change	No change
HPMCK4	1:1	No change	No change	No change	No change	No change	No change	No change	No change
HPMCK15	1:1	No change	No change	No change	No change	No change	No change	No change	No change
Tetrabenaz	755	755	755	755	755	755	755	755	755
HPMCK100	1:1	No change	No change	No change	No change	No change	No change	No change	No change
Prosolv-HD60	1:1	No change	No change	No change	No change	No change	No change	No change	No change
Colloidal silicon dioxide	1:1	No change	No change	No change	No change	No change	No change	No change	No change

Table 2: Formulation composition of sustained release matrix tablets of TBZ

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9

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ine									
HPMCK4	150	200	220	0	0	0	0	0	0
HPMCK15	0	0	0	150	200	220	0	0	0
HPMCK100	0	0	0	0	0	0	150	200	220
Prosolv-HD60	90	40	20	90	40	20	90	40	20
Aerosil	10	10	10	10	10	10	10	10	10
Mg. Stearate	8	8	8	8	8	8	8	8	8
Total	1013	1013	1013	1013	1013	1013	1013	1013	1013

Evaluation of sustained release layers:

The micromeritic properties of prepared sustained release granules were evaluated for %LOD (Loss on drying), angle of repose, bulk density and tapped density, Carr's compressibility index and Hausner's ratio.

Evaluation of sustained release tablets

The prepared sustained release tablet formulations were evaluated for hardness, thickness, friability, weight variation and drug content as per USPXXI specifications. For determination of drug content, an accurately weighed quantity of powder was taken and suitably dissolved in phosphate buffer (pH 7.4), appropriate dilutions were made and analyzed spectrophotometrically at 273 nm to calculate the percentage drug content. The acceptance criteria of all these tests were purely based on the USPXXI specifications. The sustained release tablets were also evaluated for the in vitro drug release studies, drug release kinetic evaluation, water uptake, swelling and erosion studies, and SEM.

Systematic optimization of tablets using design of experiments

The systematic optimization of the sustained release tablet formulation was carried out using a response surface design on the factors influencing the responses. A two-factor and three-levels containing central composite design was selected for optimization study. A total of 13 trial formulations were prepared and evaluated for in vitro drug release in dissolution media (0.1N HCl and pH 7.4 phosphate buffer) as the response variables. Table 4 illustrates the design matrix as per the central composite design with two factors (i.e., Eudragit L100 D55 and HPMC K4M) studied at three different levels such as low (-1), medium (0) and high (+1). All the characterization studies were performed in triplicate for accuracy of the observations.

Table 3: Design matrix indicating trial formulations of chronomodulated release

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drug release system as per the central composite design

Trials	Type of points	Factor 1 (HPMC K100M)	Factor 2 (HPMC K4M)
1	Factorial	150	150
2	Axial	50	225
3	Factorial	50	150
4	Center	100	225
5	Center	100	225
6	Center	100	225
7	Center	100	225
8	Axial	100	150
9	Center	100	225
10	Axial	100	300
11	Axial	150	225
12	Factorial	150	300
13	Factorial	50	300

Optimization data analysis and search for optimum formulation

The optimization data analysis was carried out by evaluating the response variables. Subsequently, mathematical modeling and fitting of data was performed by multiple linear regression analysis (MLRA). The appropriateness of model was evaluated using parameters like model p-value, coefficient of correlation (R) and lack of fit analysis. The response surface mapping was carried out using 3D and 2D- plots for critical understanding of the factor-response relationship. At the end, the optimum formulation was identified with the help of numerical optimization and desirability function, where target values of the responses were provided to meet the desired objectives. Moreover, the graphical optimization was also performed for locating the optimum formulation within the design space. Validation study of the selected DoE model was performed by selecting six confirmatory check-point formulations, where the observed and predicted values of the responses were compared with the help of linear correlation plots. Also, the residual graphs were plotted to calculate the percent prediction error between observed values and residuals.

Characterization of optimized tablets

***In vitro* drug release study**

The *in vitro* drug release from the prepared sustained release tablet formulations of Tetrabenzin tablets were carried out using USP Type-I dissolution apparatus (Electrolab, Mumbai, India) at 100 rpm and 37±0.5°C. The dissolution was carried out in 0.1 N HCl (pH

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1.2) up to 16 h in replicates (n=3) and percentage drug release at different time intervals were measured spectrophotometrically at 273 nm. The graph was then plotted between cumulative percentage drug release *versus* time.

Drug release kinetics modeling

The *in vitro* drug release data obtained from dissolution studies were subjected to mathematical modelling employing zero-order (Eq. 1), first-order kinetic model (Eq. 2), Higuchi square root model (Eq. 3) and Hixon-crowell model (Eq. 4).

$$Q = k_0 t \text{.....} (1)$$

Where, Q is the amount of drug released at time t, and k_0 is the release rate constant,

$$\ln(100 = Q) = \ln 100 - k_1 t \text{.....} (2)$$

Where, k_1 is the release rate constant

$$Q = k_2 t_1^2 \text{ ..... } (3)$$

Where, k2 is the diffusion rate constant

$$W0^{1/3} - Wt^{1/3} = Kt \text{..... } (4)$$

Where, W0 and Wt= Initial amount of drug present in the matrix and amount of drug release at time t, K= release rate constant

Evaluation of drug release mechanism

In order to predict the mechanism of drug release from the prepared sustained release matrix tablets, Korsmeyer-Peppa's equation (5) was applied as follows:

$$M_t / M_{\square} = Kt^n$$

Where, Mt/M∞ is the fractional solute release, t is the release time, K is the kinetic constant which is the characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of drug release. For cylindrical matrix tablets (n<0.5), the drug release follows quasi-Fickian diffusion mechanism, n=0.5 follows drug release by Fickian diffusion, 0.5 < n <1 then the drug release by anomalous diffusion, n=1 indicates Case-II Transport or typical zero-order release and n>1 indicates non-Fickian super-case II transport mechanism.

Scanning electron microscopy (SEM)

Surface morphology of the selected sustained release matrix tablet formulation before and after dissolution were analyzed by SEM. The sustained release tablets after dissolution at different time intervals (0, 3, 6, 9 h) were soaked on a tissue paper and dried under vacuum oven at 45°C

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up to 6 h. The dried tablets were subjected to gold coating and mounted on brass stubs using carbon paste and kept in a dessicator for one week. A working distance of 39 mm was maintained, and the acceleration voltage of 10kv was used with secondary electron image as the detector. Surface morphology of tablets were observed using the electron microscope (LEO 1550VP, Carl Zeiss-Leica Ltd., USA) under suitable magnification.

Evaluation of optimized chronomodulated release tablets

Optimized sustained release layers of tablet formulation were finally compressed into bilayer tablets. As per the previously reported procedure, the sustained granules release granules were weighed. Initially, the sustained release layer was filled in to the die cavity of rotary tablet punching machine and subjected to pre-compression. Then the granules were filled into the die cavity, and finally both the layers were compressed into a single bilayer tablet using punch size of 20 × 9 mm. The optimized tablets were subsequently subjected to different evaluation techniques.

General evaluation studies

The optimized bilayer tablets were evaluated for hardness, thickness, weight variation, friability study.

Accelerated stability studies

The optimized bilayer tablets were also subjected to accelerated stability study as per ICH-guidelines by suitable packaging in plastic polyethylene bottles up to 6 months. At different time periods of 1, 2, 3 and 6 months, the formulations were observed for colour, hardness, %friability, weight variation, drug content and in vitro drug release. For estimation of shelf-life, the bilayer tablets in HDPE bottles were stored at 30 ± 0.5°C, 40 ± 0.5°C and 50 ± 0.5°C temperature up to a period of three months. Samples were withdrawn after specified time intervals (0, 1, 2, 3 and 6 months), concentration and log concentration of Tetrabenzine remained was calculated. Order of reaction in which drug degradation occur was estimated. The reaction rate constant (K) for the degradation was measured from slope of lines at each elevated temperature using equation (9), and an Arrhenius plot was constructed (i.e., plot of log K at various elevated temperatures against the reciprocal of absolute temperature). From the plot, K value at 25°C was determined and used for prediction of shelf-life by substituting in equation (10)

$$Slope = -K/2.303 \ldots\ldots\ldots (9)$$

$$t_{90} = 0.1053/ K_{25} \ldots\ldots\ldots (10)$$

Table 4: Target product profile (TPP) of chronomodulated release drug delivery systems of Tetrabenzine

TPP Elements	Target	Justification

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Dosage design type	Chronomodulated release	Helps in maintaining the therapeutic effect of drug for prolonged periods of time by maintaining optimal drug release at predefined time intervals.
Dosage form type	Bilayer matrix tablet	Selection of a bilayer tablet with a floating and a sustained release layer provides time- dependent drug release characteristic for reducing the bacterial population growth as a chronokinetic phenomenon
Route of administration	Oral	Oral route is recommended for delivery of Tetrabenzine and available marketed formulations are also meant for oral intake only.
Dosage strength	50 mg	It is the unit dose of Tetrabenzine needs to be deliver for once-a-daily administration
Packaging	PVC blister	The tablet formulations can easily be delivered by packing in PVC blister for patient compliance, portability and manufacturing ease
Stability	At least 24 months at room temperature	To maintain therapeutic potential of the drug during storage period

RESULTS AND DISCUSSION

Defining target product profile (TPP)

Table 5 summarizes the target product profile of chronomodulated release drug delivery systems of Tetrabenzine. As per the QbD principles, a summary of the quality characteristic of the designed dosage form has been provided.

Drug-excipient compatibility studies

Solid state characterization using FT-IR and DSC studies revealed lack of any significant interaction between drug and excipients. FT-IR spectra of drug- excipient mixture stored at different temperature conditions were compared with spectrum of pure drug revealed no change in characteristic peaks of the drugin all solid admixtures are shown in Figure 1, which indicated absence of change in the peak area of the drug. Similarly, no significant change in the endothermic melting peak of drug-excipient mixture under DSC further supported lack of interactions (Figure 2).

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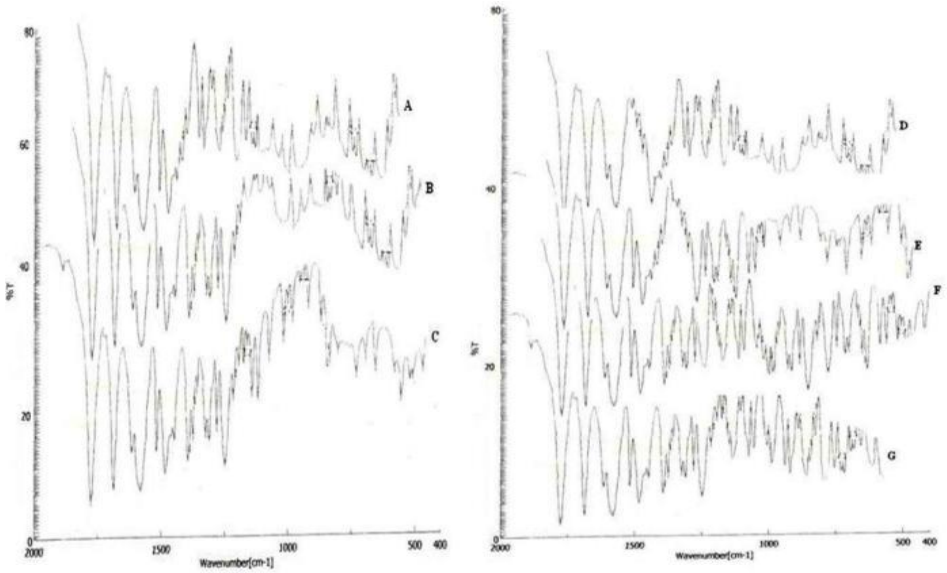

Fig. 1: Drug-excipient compatibility studies by FT-IR spectra, (A) Pure drug; (B) Drug+HPMCK4M; (C) Drug+Eudragit-L100D55

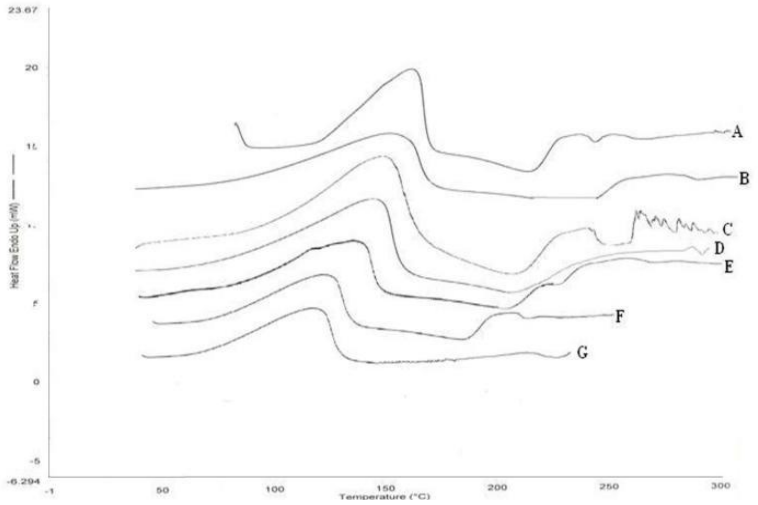

Fig. 2: DSC thermograms of pure drug and its physical mixture with polymer materials, (A) Pure drug (TBZ); (B) Drug+HPMCK4M; (C) Drug+Eudragit L100 D55; (D) Drug+Prosolv HD60; (E) Drug+Aerosil 200, (F) Dug+Magnesium Stearate; (G) Composite mixture of drug with all the excipients

Evaluation sustained release granules

Evaluation of sustained release granules Micromeritic characterization

The % LOD of all batches of sustained release granules were found to be less than 13% due to the hydrated nature of the drug, represented that the prepared granules were dried. All other micromeritic properties like angle of repose between (25-30%), Carr's index between (13-22%)

and Hausner's ratio (<1.3) for sustained release granules indicated good flow property and compressibility characteristics.

Technological characterization

Various technological characterization of sustained release tablets including hardness, thickness, friability, weight variation and drug contents are shown in Table 7**.** Results showed that all formulations passed the USP limits for various quality control tests. The hardness challenge test showed that tablets prepared with Hypromellose K4M were found to be quite harder at normal compression pressure because granulation with Hypromellose is rubbery in nature, which provides high hardness after compression owing to negligible elastic deformation.

Table 5: Granulometry data of sized sustained release granules

Formulation code	F1	F2	F3	F4	F5	F6			
Loss on drying (%)	12.5	12.2	12.7	12.8	12.6	12.9			
Bulk density (g/cc)	0.58	0.63	0.65	0.68	0.69	0.71			
Bulk density (g/cc)	0.74	0.79	0.78	0.81	0.82	0.83			
Hausner's ratio	1.28	1.25	1.2	1.19	1.19	1.17			
Carr's index	21.62	20.25	16.67	16.05	15.85	14.46			

Evaluation of sustained release tablets

The prepared sustained release tablets showed good physical appearance with hardness, thickness, friability, weight variation and drug content with in the acceptable pharmacopoeial limits as enlisted under Table 7. Results indicated that all batches of prepared tablet formulations were met the USPXXI specifications with thickness <5%, hardness 13 kg/cm2, friability <1% and weight variation within ±10. Drug content uniformity was within 98.9 ± 0.35 to 102.4 ± 0.16%, respectively.

Table 6: Technological characterization of sustained release tablets of TBZ (Mean ± S.D, n=6)

Formulation code	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**	**Weight variation (mg)**	**Drug content**
F1	5.2 ± 0.02	13.4 ±0.06	0.9	901 ± 0.06	100 ± 0.04

F2	5.1 ± 0.04	13.2 ±0.04	0.61	904 ±0.08	98.91 ±0.14
F3	5.3 ± 0.07	12.9 ±0.03	0.54	901 ±0.03	100.5 ±0.07
F4	5.0 ± 0.00	13.4 ±0.06	0.55	904 ±0.07	101.9 ±0.06
F5	5.2 ± 0.06	13.2 ±0.08	0.65	898 ±0.12	101 ±0.06
F6	5.4 ± 0.08	13.3 ±0.09	0.52	900 ±0.07	98.91 ±0.35
F7	5.6 ± 0.10	12.4 ±0.12	0.64	905 ±0.07	99.4 ±0.12
F8	5.2 ± 0.02	13.6 ±0.09	0.72	884 ±0.1	100 ±0.03
F9	4.9 ± 0.08	13.1 ±10	0.41	902 ±0.12	102 ±0.16

In vitro drug release studies

In vitro drug release studies of the prepared sustained release tablets signified that HPMC based formulations have good sustained action. Figure 4 illustrates the *in vitro* drug release profile of the tablet formulations prepared using sustained release granules. Several factors such as nature of polymer, concentration of polymer, compression force applied, water uptake capacity, swelling and erosion tend to affect the drug release behaviour. Figure 4(a) depicts *in vitro* drug release profile of the formulation F1-F3 containing HPMCK4M as rate-controlling polymer in the concentration ranging between 50 to 70 mg. The formulations showed good sustained release action up to 16 h, with initial drug release in the first three hour varied from 25 to 27%, respectively. Figure 4(b-c) represents the comparative *in vitro* drug release profile of formulation F4-F6 and F7-F9. These formulations containing HPMCK15 and HPMCK100 in the concentration of 50 to 70 mg, also showed good sustained action up to 20 h and 24 h, respectively. The drug released in first three hour varied from 19 to 25 % in HPMCK15 and 16 to 25% with HPMCK100. This confirmed that the drug release was decreased both by the increased concentration and viscosity of the polymer and the formulations containing lower viscosity grades of HPMC showed faster drug release vis-à-vis higher viscosity grade polymers. It has been reported that increase in the polymer concentration increases the gel strength, while increase in viscosity increases swelling tendency and formation of gel layer with longer diffusional path length. Hence, the formulations prepared with HPMCK100 showed higher sustained action as compared to formulations containing HPMCK15 and HPMCK4M.

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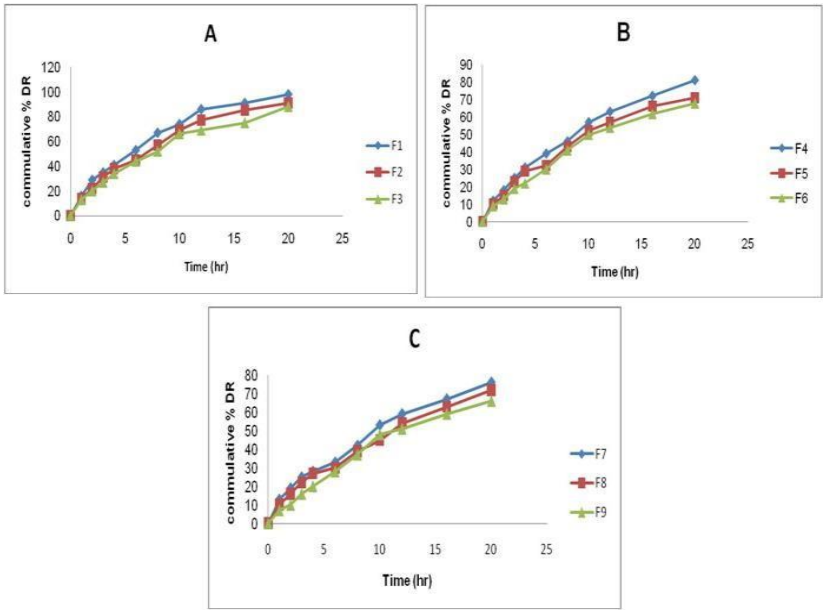

Fig. 3: Comparative in vitro drug release profiles of different batches of sustained release tablets, (A) F1-F3 with HPMCK4M (B) F4-F6 with HPMCK15 (C) F7-F9 with HPMCK100

Search for the selection of optimized formulation

The optimized time-dependent release bilayer tablet formulation was identified by numerical optimization by selecting the desired ranges for the response variables as shown in Table 8.

Table 8: Constraints of the responses selected for numerical optimization

Constraints			
Name	**Goal**	**Lower Limit**	**Upper Limit**
A:HPMC K100M	is in range	50	150
B:HPMC K4M	is in range	150	300
Dissolution in 2 h	is in range	5	19
Dissolution in 4 h	is in range	29	54
Dissolution in 8 h	is in range	42	67
Dissolution in 16 h	is in range	67	84
Dissolution in 24 h	is in range	83	93

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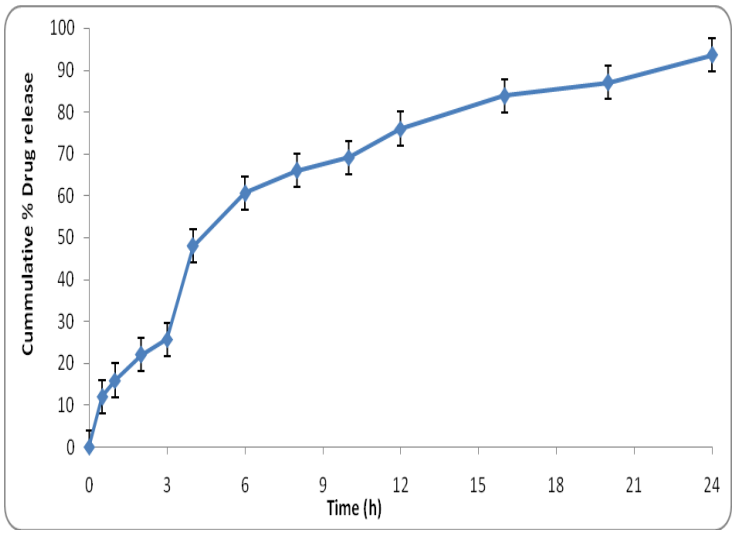

Fig. 4: In vitro drug release profile of TBZ tablets

Evaluation of drug release kinetic

In vitro drug release data for the optimized bilayer formulation was fitted to various kinetic models which indicated higher values of coefficient of correlation (r2) with Higuchi's square root model as 0.951. The "n" value was found to be 0.419, indicated drug release by quasi-Fickian diffusion (n<0.5), where the drug release is controlled by combined action of diffusion along with polymer chain relaxation process.

Accelerated stability studies

The accelerated stability studies revealed that there was no significant change in the various physical characterization parameters like color, hardness, friability, weight variation and assay of optimized bilayer tablet formulation. The dissolution profile revealed that there was no change in the in vitro drug release behaviour. The present studies successfully embarked upon formulation of once-a-daily optimized chronomodulated release bilayer matrix tablet formulations of TBZ. The developed formulation showed satisfactory drug release profile to maintain the concentration of drug throughout the day which helps in reducing the MIC value of the drug. The drug release profiles from the formulations were successfully fitted to mathematical modeling for predicting the drug release kinetics. The drug releases from the sustained layer followed Higuchi model owing to drug release predominantly by diffusion and surface erosion phenomenon. The microbiological studies confirmed the decrease in MIC and enhanced antimicrobial activity owing to gastric protection of the drug and programmed site-specific drug release. The promising outcomes of present studies on TBZ can be extrapolated successfully to other antimicrobial agents acting on the diseases whose progression depend on the circadian rhythm of body.

CONCLUSION:

The floating tablet was found to be a promising approach for controlled release. Gel forming and mucoadhesive polymer like HPMC K15M, Xanthan gum 180, Carbopol 974P NF, and polyethylene oxide N80 and effervescing sodium bicarbonate along with citric acid added to the formulation are essentially required to achieve *in-vitro* buoyancy, desirable drug release, and excellent bioadhesive strength. The formulation retained a longer period of time floated in 0.1N HCl and provided sustained release of drug from the formulation. Hence it may increase the therapeutic efficacy of the drug by increasing the bioavailability and patient compliance.

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