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Original Article

DEVELOPMENT AND EVALUATION OF BILAYER MUCOAHESIVE GASTRORETENTIVE TABLET OF DILTIAZEM HYDROCHLORIDE

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ABSTRACT

Objective: The objective of present study was to formulate an oral mcoadhesive tablet of diltiazem hydrochloride.

Methods: Investigate the effect of amount of HPMC K4M and sodium alginate on the sustained release and gastric residence time of dosage form. The mucoadhesive tablet prepared by direct compression method was used varying concentrations of HPMC K4M and Sodium alginate and (1:1, 1:1.5, 1:2) Drug and Polymer ratio.

Results: The formulations were evaluated and results revealed that FTIR studies showed no evidence of interactions between drug and excipients used. The mucoadhesive strength, residence time and drug content of formulation F3 was found to be 26.35 ± 1.15 mg, >7.5hrs, and 98.75 ± 0.05 % respectively. The formulation F3 exhibited sustained drug release i.e. 75.71% in 12 h. The *In Vitro* release kinetics studies reveal that formulations fit well with zero order kinetics and mechanism of drug release is Super case II transport.

Conclusion: The study was concluded that formulation of mucoadhesive tablets from the cumulative % drug release study reveals that increase in the concentration of adhesive polymers cause slow the drug release. Sustained release tablet of DTZ can be beneficial in treatment of hypertension.

Keywords: Diltiazem Hydrochloride, Mucoadhesive tablet, Sodium alginate, Mucoadhesive strength, *In Vitro* drug release.

INTRODUCTION

Oral drug delivery route is the most preferable route of drug delivery. It is due to various advantages of this route like ease of administration, patient compliance and flexibility in the formulations. Oral absorption of drugs is often limited due to short gastric retention time. The gastric retention time is 3 to 4 hrs of human beings. The retention of drug delivery system in the stomach prolongs overall Gastrointestinal (GI) transit time, there by resulting in improved bioavailability drugs. However, oral route has certain problems such as unpredictable gastric emptying rate, short gastro-intestinal transit time and existence of an absorption window in the gastric and upper small intestine for several drugs [1-2].

Polymers can be used to control the release of both water soluble and water insoluble drugs. On the surface, their drug release behavior appears simple, but the drug release pattern is a complex phenomenon. At the molecular level, it involves water penetration, polymer adhesion as well as drug dissolution, diffusion and polymer erosion process [3-6]. Various approaches for gastroretentive dosage forms have been proposed including mucoadhesive, swellable and floating systems [7-8]. Diltiazem hydrochloride is a calcium channel blocker, which has been used in the treatment of cardiovascular disorders, particularly angina pectoris and systemic hypertension. It has short biological half life of about 3.5 h and rapidly eliminated. It is favorably absorbed from stomach and the oral bioavailability is about 40% [9-10].

The sustained gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape system or by the simultaneous administration of pharmacological agent that delay gastric emptying rate[11-13].

The objective of the present work was to develop mucoadhesive tablet of Diltiazem hydrochloride, which after oral administration could prolong the gastric residence time and increase its bioavailability. After oral administration, such stomach-specific mucoadhesive tablets would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of stomach-specific mucoadhesive tablets for these drugs [14-16]. Mucoadhesive tablets are widely used because they release the drug for prolong period, reduce frequency of drug administration and improve the patient compliance [17].

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was procured from Nicholas Piramal Ltd., Mumbai. Hydroxy propyl methylcellulose (HPMC K4M) was supplied by Colorcon Ltd., Goa, Sodium alginate was gifted by Snap Natural and Alginate products Pvt. Ltd., Tamilnadu, Polyvinyl pyrrolidone K30 was procured from Spectrochem Pvt. Ltd, Mumbai, and all the other chemicals used were of analytical grade.

Experimental

Preformulation study

The sample of Diltiazem hydrochloride was analyzed for its nature, color and taste. The melting point was done by capillary tube method. Diltiazem hydrochloride was estimated by UV spectrophotometry method.

Infrared spectra analysis

Infrared spectrum of DTZ was determined on Fourier Transform Infrared Spectrophotometer (FTIR Shimadzu -4100) using KBr dispersion method. The base line correction was done using dried potassium bromide. The spectrum of dried mixture of drug and potassium bromide (1:100) was obtained.

Compatibility studies

The FTIR spectra's are used to identify the drug and detect the interaction of drug and polymers. FTIR spectrum of pure drug and physical mixture of drug and polymers were obtained on FTIR (Shimadzu 4100) instrument. The physical mixture of drug and polymers was prepared (1:1) and spectrum of physical mixture and potassium bromide (1:100) was obtained.

Preparation of mucoadhesive tablet

The mucoadhesive gastroretentive tablets were prepared by direct compression method using rotary tablet machine (Rimek, Mumbai). The proportionate composition of various ingredients was given in table 1. The hydrophilic polymers like HPMC K4M and Sodium alginate were used as mucoadhesives agents in the formulation. Lactose and Polyvinyl pyrrolidone K30 were used as diluents and binder respectively. Magnesium stearate and Ethyl cellulose were used as lubricant and as backing layer. All ingredients were mixed thoroughly and the tablets were directly compressed by using a rotary tablet machine of 13 mm punch size.

Characterization of granules properties

The granules were evaluated for their characteristic parameters, such as bulk density, tapped density, Carr's index and angle of repose. Carr's compressibility index was calculated from the bulk and tapped densities using a digital tap density apparatus (Electrolab Ltd, India) [18-19].

Compression of tablet

The quantity of excipients was compressed lightly using a minipress rotatory tablet machine, equipped with 10 mm round, flat and plain punches for core tablet and bilayer coating with ethyl cellulose by using 13 mm punches size.

Physical tests for the tablets

The standard physical tests for the tablets were performed and average weight was calculated. Thickness and diameter were measured using vernier caliper. Hardness was determined by using a Monsanto hardness tester (Electrolab Pvt. Ltd., India) and the average of pressure (kg/cm^2) applied for crushing the tablet was determined.

Friability was determined by using friability tester apparatus (Veego Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of the tablets was recorded and the percent friability was calculated.

Drug content uniformity

Ten tablets were finely powdered and an amount equivalent to 10 mg was accurately weighed and dissolved in 10 ml 0.1N HCl with the help of sonication for 20 min. The resulting solution was further diluted with 0.1N HCl to achieve concentration up to 10 µg/ml and the absorbance measured at the 237 nm using double beam UV spectrophotometer.

Table 1: Composition of Mucoadhesive Tablets of DTZ.

Ingredients	Batches codes					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
DTZ HCl	100	100	100	100	100	100
HPMC K4M	100	150	200	_	_	_
HPMC E15	_	_	_	100	150	200
Sodium alginate	125	75	25	125	75	25
Lactose	70	70	70	70	70	70
PVP k30	60	60	60	60	60	60
Magnesium stearate	5	5	5	5	5	5
Core tablet	460	460	460	460	460	460
Layer 2 EC	100	100	100	100	100	100
Total weight	**560**	**560**	**560**	**560**	**560**	**560**

***In Vitro* drug release study**

The *In Vitro* dissolution was carried out by using Dissolution Testing apparatus type II. The tablet was placed to the dissolution medium (900 ml) of 0.1N HCl. Dissolution medium temperature was maintained at 37°C and stirring at 100 rpm. An aliquot of the sample (5 ml) was periodically withdrawn at hourly for 12 hours and the volume was replaced with fresh dissolution medium. The samples were analyzed spectrophotometrically at 237 nm. The cumulative percentage drug release was calculated [20-23].

Ex- vivo mucoadhesive characteristics

Ex vivo mucoahesive strength

The working of a double beam physical balance formed the basis of the mucoadhesion test. The two pan of a physical balance was removed and replaced with a same volume of beakers hanged with a lightweight thread. The height of this total set-up was adjusted to accommodate a glass petriplate below it, leaving a head space of about 0.5 cm in between petriplate and left beaker. The two sides were then balanced. The sheep mucus membrane was excised and washed (equilibrated at 37ºC ± 1ºC for 30 min in 0.1N HCl medium before the mucoadhesion evaluation study) and tied tightly with the thread to mucus on glass side, which was then filled with 0.1N HCl kept at 37ºC ± 1ºC, such that 0.1N HCl just reaching the surface of mucosal membrane and keeping it moist. This was then kept below the left beaker and the left beaker was then lowered into the petriplate of the balance. The tablet was then stuck to the bottom of left beaker, using two way adhesive and the balance beam. A constant weight of 10 gm was then placed over the left beaker for the total contact of tablet to mucus for a period of 5 min. Mucoadhesive strength was then assessed by adding weights on the right beaker till the tablet separated from the mucosal surface, in terms of the weight (in gm) required to detach tablet from the membrane. The modified physical double beam balance was shown in figure 1 [25-26].

Fig. 1: Modified physical double beam balance

Ex vivo residence time

The ex vivo residence time was carried out by using disintegration test apparatus. The disintegration medium was composed of 800 ml of 0.1N HCl maintained at 37°C. The sheep stomach mucosa or epithelial cell was tied to the surface of a glass slab using thread, vertically attached to the apparatus. The mucosal tablet was hydrated from one surface using 0.5 ml of 0.1N HCl and then the hydrated surface was brought in contact with the mucosal membrane. The glass slide was vertically fixed to the apparatus and allowed to run in such way that the tablet completely immersed in the 0.1N HCl at the lowest point. and was out at the highest point.

The time taken for complete erosion or dislodgment of the tablet from the mucosal surface was noted. Disintegration test apparatus was shown in figure 2 [27].

Fig. 2: Disintegration test apparatus

Differential scanning calorimetry (DSC)

The Differential Scanning Calorimetric analysis was carried out using SDT 2960 TA Instrument, USA, Differential Scanning Calorimeter. Samples were placed in a platinum crucible and the DSC thermograms were recorded at a heating rate of 10ºC/min in the rage 20º to 350 ºC, at a nitrogen flow of 20 ml/min [28].

Powder x-ray diffraction (PXRD)

The Powder X ray Diffraction (PXRD) was carried out using Philips X-ray diffracto-meter, PW-3710, Holland, using Cu Kα radiation (λ = 1.5405 Å) at voltage of 40 kV, and 30 mA current. The data recorded over a range of 10°c to 50°c at a scanning rate of 5×103 cps using a chart speed of 5 mm/2°c [29-30].

Scanning electron microscopy

The morphology of the surface of tablet before and after dissolution was studied for understands the mechanism of drug release and expansion by using scanning electron microscopy. The intact tablet was scanned before and after dissolution for 6 hours, tablet was removed and dried to remove water content.

The sample was coated with a gold-palladium target using a Navatec (JEOL JSM-6360 SEM, Japan) vacuum evaporator for 1 hour. SEM image was obtained at an acceleration voltage of 8 to 10 kV. [34-35].

Stability study

The batch F3 was selected as an optimized batch for the stability study. Five tablets were individually wrapped using aluminum foil and packed in amber color screw cap bottle and kept at specified conditions of 40 °C at 75 % RH for the period of three months. The dissolution profile was analyzed after three months [36].

RESULT AND DISCUSSION

The sample of Diltiazem hydrochloride was crystalline powder having off white to white color, odorless and bitter in taste. The melting point was observed in the range of 212°C– 215°C. The standard solution of Diltiazem hydrochloride was scanned through 200-400 nm regions on Jasco V-530 UV spectrophotometer. The Diltiazem hydrochloride absorption maximum was found to be 237 nm. FTIR spectrum of pure drug was found to be similar to that of standard spectrum of DTZ. It showed characteristics peaks belonging to measure functional groups shown in figure 3.

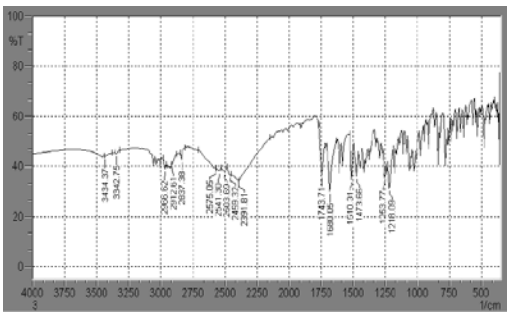

Fig. 3: FTIR spectral analysis of DTZ

Compatibility Studies

FTIR studies revealed that the fundamental peaks of the DTZ HCl are retained in the physical mixture. Results showed that there exist no chemical interaction between DTZ HCl and polymer and excipients, hence; these can be used in the formulation of mucoadhesive tablet of DTZ HCl. Overlain spectrums of pure drug (DTZ HCl), HPMC K4M, and physical mixture of drug and polymer were shown in figure 4.

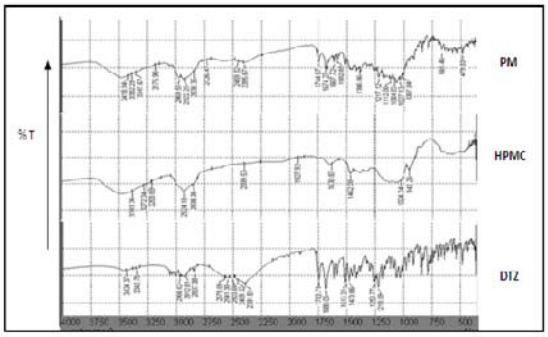

Fig. 4: Overlain FTIR spectrums of DTZ, HPMC K4M, PM (physical mixture)

Evaluation of powder properties

The bulk density of powder mixture was found to be between 0.3105 ± 0.04 to 0.3408 ± 0.02 g/cm^3. This indicates good packing capacity of powder. Carr's index was found to be between 16.56 ± 0.04 to 20.13 ± 0.10 % show good flowability. Hausner's ratio was less than 2 that indicates good flowability. The angle of repose was in range of 18.08 ± 0.17 to 20.13 ± 0.10 % show excellent flowability of the powder mixture. The powder properties of DTZ tablet formulation shown in table 2.

Table 2: Powder properties of all batches

Batch code	Bulk density (g/cm^3)*	Tapped density (g/cm^3)*	Carr's Index (I_C)*	Hausner's Ratio (H_R)*	Angle of Repose (θ)*
F1	0.3335 ± 0.04	0.4176 ± 0.04	20.13 ± 0.10	1.25 ± 0.02	19.76 ± 0.14
F2	0.3262 ± 0.01	0.3958 ± 0.01	17.58 ± 0.12	1.21 ± 0.04	19.46 ± 0.14
F3	0.3125 ± 0.04	0.3850 ± 0.02	18.83 ± 0.02	1.20 ± 0.04	18.36 ± 0.12
F4	0.3408 ± 0.02	0.4166 ± 0.04	18.19 ± 0.06	1.22 ± 0.03	17.67 ± 0.13
F5	0.3309 ± 0.01	0.3966 ± 0.03	16.56 ± 0.04	1.19 ± 0.06	18.08 ± 0.17
F6	0.3105 ± 0.04	0.3846 ± 0.02	19.26 ± 0.04	1.23 ± 0.02	21.96 ± 0.14

∗ Indicates average reading ± SD (n = 3)

Evaluation of mucoadhesive tablets of DTZ

The average weight of tablets and thickness were ranged from 558.1 ± 1.6 to 560.5 ± 0.7 mg and 4.03 ± 0.07 to 5.75 ± 0.05 mm respectively. The diameter and hardness were ranged in between 13.01 ± 0.01-13.10 ± 05 mm and 7.15 ± 0.5 to 8.40 ± 0.2 kg/cm^2. The friability was in range of 0.0026 ± 0.04 to 0.0053 ± 0.04 %. Drug content was in range of 97.15 ± 0.15 to 99.45 ± 0.05 indicating good content uniformity in the prepared formulation. The values of

uniformity of weight, thickness, diameter, hardness, friability, drug content from batch F1 to F6 are shown in table 3.

Table 3: Tablet properties of DTZ mucoadhesive tablets

Batch code	Average wt (mg)*	Thickness (mm)*	Diameter (mm)*	Hardness (kg/cm2)*	Friability (%)*	Drug content (%)*
F1	558.5 ± 1.5	4.83 ± 0.02	13.02 ± 0.04	7.35 ± 0.15	0.0053 ± 0.02	98.65 ± 0.05
F2	559.5 ± 1.0	4.85 ± 0.05	13.01 ± 0.01	7.15 ± 0.40	0.0035 ± 0.05	97.60 ± 0.15
F3	560.1 ± 0.6	4.88 ± 0.02	13.01 ± 0.03	8.33 ± 0.20	0.0026 ± 0.04	98.75 ± 0.05
F4	559.5 ± 0.8	4.85 ± 0.05	13.05 ± 0.05	8.44 ± 0.10	0.0035 ± 0.05	97.15 ± 0.15
F5	558.1 ± 1.6	4.80 ± 0.04	13.01 ± 0.01	7.27 ± 0.25	0.0053 ± 0.04	98.45 ± 0.10
F6	560.5 ± 0.7	4.86 ± 0.04	13.03 ± 0.08	8.31 ± 0.20	0.0026 ± 0.04	99.45 ± 0.05

∗ Indicates average reading ± SD (n = 3)

In Vitro drug release study

The *In Vitro* dissolution study, was concluded that release drug from the matrix is largely dependent on the polymer adhesion, drug diffusion and matrix erosion. It was observed that all the tablets were having lag time for first one hour and after first hour it adhere until the complete of release studies. The drug release study was carried out under specified conditions up to 12 hrs. The cumulative % drug release of F1 to F6 batch was in the range 75.71 ± 1.12 to 91.52 ± 1.08 %. The higher concentration of polymer resulted in the retardation or decreases the drug release. The batch F3 showed 75.71 ± 0.29 % for 12 hrs, which shows sustained release pattern. Hence, batch F3 was selected as optimized batch considering sustained release of drug. The cumulative % drug release of batch F1 to F6 shown in figure 5

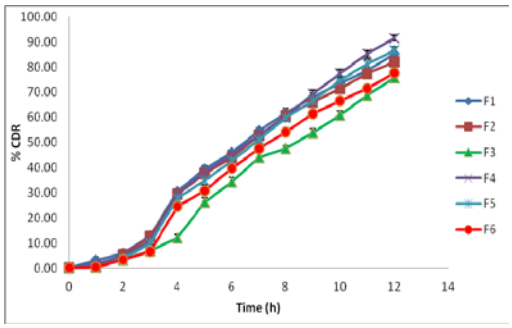

Fig. 5: *In Vitro* drug release of batch F1 to F6

The mean diffusional exponent values (n) ranged from 1.1439 to 1.3404 indicating that all the formulations presented a dissolution behavior controlled by Super case II transport. While the kinetic constant (k) ranged from 3.1300 to 5.7320 indicating that DTZ release from hydrophilic binder matrices followed super case II transport. The correlation coefficient revealed that zero order models were better applicable to release data for all the batches. The release kinetic model was shown in table 4.

Table 4: Release kinetics model of batch F1 to F6

Batch code	N	k	R	Best fit model
F1	1.1439	5.7320	0.9922	Zero Order
F2	1.2707	4.3341	0.9921	Zero Order
F3	1.3174	3.1300	0.9897	Zero Order
F4	1.2484	4.6828	0.9937	Zero Order
F5	1.3404	3.7147	0.9924	Zero Order
F6	1.3282	3.4315	0.9902	Zero Order

Ex-vivo mucoadhesive strength and residence time determination

The mucoadhesive strength and residence time was in the range of 17.15 ± 2.35 to 26.35 ± 1.15 gm and < 5.5 hrs to > 7.5 hrs respectively. The values of mucoadhesive strength and residence time were shown in table 5.

Table 5: Ex-vivo mucoadhesive strength and residence time

Batch no.	Mucoadhesive Strength (gm) ∗	Residence Time (in hr)
F1	18.20 ± 2.30	< 6.0 hrs
F2	23.80 ± 1.20	< 7.0 hrs
F3	26.35 ± 1.15	> 7.5 hrs
F4	17.15 ± 2.35	< 5.5 hrs
F5	22.65 ± 2.15	< 6.5 hrs
F6	25.45 ± 1.05	< 7.0 hrs

∗ Indicates average reading ± SD (n = 3)

Fourier Transfer Infra Red Spectrophotometer

FTIR studies revealed that the fundamental peaks of the DTZ HCl were retained in the optimized formulation and physical mixture. The results showed that no chemical interaction between DTZ HCl and excipients used in the formulation. Overlain spectrums of pure drug DTZ HCl, HPMC K4M, physical mixture and optimized batch F3 were shown in figure 6.

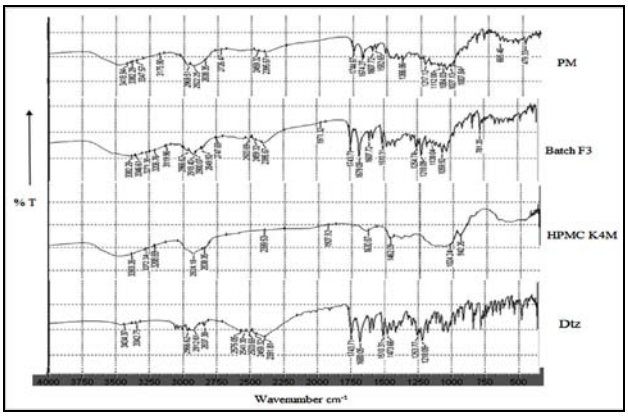

Fig. 6: Overlain FTIR spectrums of DTZ, HPMC K4M, optimized batch F3, PM (physical mixture)

Differential scanning calorimetry

The thermogram of pure DTZ HCl shows sharp endothermic peak starting at 209 °C with melting peak at 214.10°C and in the thermogram of optimized batch, endothermic peak was obtained at 212.60°C. Slight shifting of endothermic peaks with decrease in its intensity indicates somewhat reduce crystallinity of drug. Another peak observed in formulation at 74.70 °C may be due to polymers present in it. Thermographs of DTZ HCl and optimized tablet shown in figure 7.

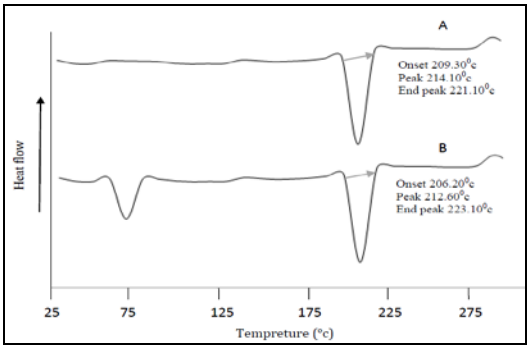

Fig. 7: DSC overlain of (A) DTZ, (B) batch F3

Powder X-ray diffractometry

Powder X-ray diffraction study reveals that the intensity of the peaks for the pure drug was sharp, but when it was incorporated into the polymer matrix, the intensities of the peaks decreases due to decreased crystallinity of the DTZ HCl.

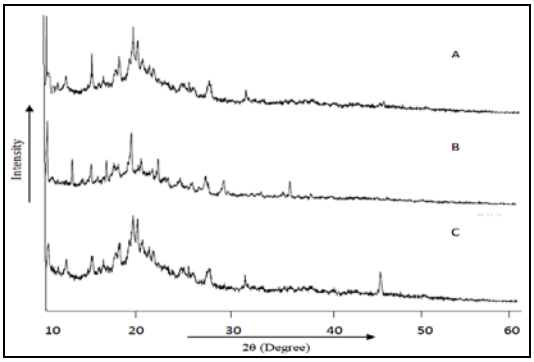

Fig. 8: PXRD Overlain of DTZ (A), physical mixture (B), optimized batch F3(C)

Thus, it was observed that reduction in the crystallinity of drug in the optimized batch F3. The overlain of PXRD pattern of DTZ HCl, physical mixture and optimized batch F3 has been shown in figure 8.

Scanning electron microscopy

The SEM photomicrograph of the tablets after dissolution showed a highly porous tablet surface and also reflects a porous tablet matrix structure. This would facilitate diffusion of drug from the tablet core to the surface. The formation of both pores and gel structure on the tablet surface indicates involvement of both erosion and diffusion mechanisms for sustained drug release. The SEM images of the tablet were taken before and after dissolution shown in figure 9.

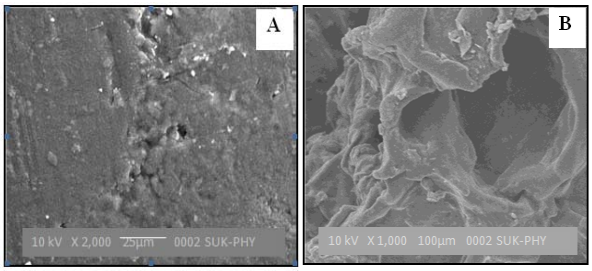

Fig. 9: SEM of optimized batch F3 before dissolution (A) and after dissolution (B)

Stability study

The stability study was carried out at accelerated conditions of 40°C / 75% RH for three months. There was no change in physical appearance in the optimized batch F3 over a period of three months. There was no significant change in the percentage release of drug after three months indicating that stable the formulation. The results of stability study after three months were shown in table 8.

Table 8: Cumulative % drug release for stability study of batch F3

Time (hour)	Cumulative % Drug Release (Initial) *	Cumulative % Drug Release (After 1 months) *	Cumulative % Drug Release (After 2 months) *	Cumulative% Drug Release (After 3 months) *
1	0.27 ± 0.06	0.25 ± 0.04	0.22 ± 0.03	0.18 ± 0.02
2	3.32 ± 0.18	3.12 ± 0.15	3.08 ± 0.12	2.98 ± 0.12
3	6.86 ± 0.50	6.12 ± 0.18	6.04 ± 0.26	5.89 ± 0.11
4	12.06 ± 1.20	11.48 ± 1.12	11.39 ± 1.06	11.08 ± 1.12
5	26.26 ± 1.20	26.12 ± 1.04	25.98 ± 1.02	25.76 ± 1.14
6	34.39 ± 1.01	34.10 ± 1.21	33.96 ± 1.14	33.69 ± 1.11
7	44.01 ± 1.09	43.75 ± 1.25	43.68 ± 1.32	43.41 ± 1.19
8	47.44 ± 0.56	47.26 ± 0.62	47.09 ± 0.51	46.89 ± 0.31
9	53.71 ± 1.04	53.60 ± 1.01	53.37 ± 1.13	53.13 ± 1.07
10	60.73 ± 1.27	60.15 ± 1.07	60.03 ± 1.07	59.84 ± 1.16
11	68.80 ± 1.20	68.33 ± 1.17	68.18 ± 1.12	68.02 ± 1.08
12	75.71 ± 1.12	75.47 ± 1.13	75.23 ± 1.17	75.09 ± 1.11

* Indicates average reading ± SD (n = 3)

CONCLUSION

The present study was to formulation of mucoadhesive tablets using direct compression method. *In Vitro* dissolution study the results reveal that increase in the concentration of adhesive polymers leads to sustained release of drug. For the sustained release of drug, optimum level of concentrations of polymers are required. DTZ release from hydrophilic matrices indicated Super case II transport and the best fit model for all batches was Zero order model. It was concluded that the development mucoadhesive gastroretentive, once a day sustained release tablet of DTZ, can be beneficial in treatment of hypertension.

CONFLICT OF INTERESTS

Declared None

ACNOWLEDGEMENTS

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