IJPSR (2016), Vol. 7, Issue 10 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 May, 2016; received in revised form, 17 June, 2016; accepted, 27 July, 2016; published 01 October, 2016

DESIGN OF CORE COMPRESSED TABLETS OF AZITHROMYCIN AND BROMHEXINE HYDROCHLORIDE AS DUAL RELEASE SYSTEM

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Keywords:

Dual Drug Delivery System, Bromhexine Hydrochloride, Azithromycin, Floating Time, HPMC

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ABSTRACT: Bromhexine hydrochloride, mucolytic agent used in the treatment of respiratory disorders. Azithromycin is use in wide variety of bacterial infections. The aim of this present work is to formulate dual drug delivery system containing azithromycin as immediate release and bromhexine hydrochloride as sustained release action. The sustained release part as core tablet of bromhexine prepared because of the frequent daily dosing is required for therapy. The floating formulation of core tablet was prepared because it dissolved in the pH range of 1 to 4. The core tablets of bromhexine hydrochloride were prepared by wet granulation technique. The prepared core tablets were evaluated for different parameters for selection of formula for floating the tablets. The core compressed tablets were evaluated for quick release of coat layer containing disintegrants. The various formulations of core tablets were prepared using HPMC K4M and K15M in different concentration. The prepared tablets were evaluated for physical parameters, disintegration time, floating lag time and drug release study. All the batches show around 70 sec disintegration time, 90 sec floating lag time and drug release up to 12 hrs. In batch B5 containing 30% of HPMC K15M found adequate drug release of bromhexine hydrochloride up to 12 hrs.

INTRODUCTION: Dual drug delivery systems are design to release drug at two different rates or in two different periods. This type of system is used when one drug require immediate release and one drug for sustained release effect to get best therapeutic response [1]. The solid oral dual drug delivery can be possible by compressed matrix core tablet, bi-layer tablet, matrix tablet/capsule containing SR granules & IR granules.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(10).4055-63

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (10).4055-63

The core-compressed tablet is an innovative approach for immediate release of drug from outer coat and sustained release of drug from inner matrix tablet.

The purpose of the present research was to produce quick and slow release biphasic system of azithromycin and bromhexine hydrochloride for upper respiratory tract infections. Upper respiratory tract infections are the illnesses caused by an acute infection which involves the upper respiratory tract: nose, sinuses, pharynx or larynx[2]. Bromhexine is a mucolytic agent used in the treatment of respiratory disorders associated with viscid or excessive mucus. In addition, bromhexine has antioxidant properties [3]. The sustained release core tablet of bromhexine prepared because of the

frequent daily dosing (2 to 3 times per day) is required for therapy of URTI. The floating formulation of core tablet was prepared because it dissolved in the pH range of 1 to 4 and the low solubility in lower region of the gastrointestinal tract [4]. Azithromycin is a semisynthetic macrolide antibiotic, which is commonly used for a wide variety of mild-to-moderate bacterial infections. Azithromycin is used to treat or prevent certain bacterial infections, most often those causing middle ear infections, strep throat, pneumonia, typhoid, and sinusitis [5].

Immediate release coat layer can be design by using super disintegrants like sodium starch glycolate, crospovidone. Sustained release part can be design by using matrix type of core tablet containing suitable polymers that can float the core tablet. Crospovidone is easily available and cheap. HPMC is a semisynthetic derivative of cellulose, which is swellable and hydrophilic in nature. It is very suitable to use as a retardant material in sustained release matrix formulations with floating properties due to formation of low density swallowable matrix [6].

MATERIALS AND METHODS:

Bromhexine hydrochloride obtained as gift sample from Orex Pharma Pvt Ltd, Thane, India. Azithromycin obtained as gift sample from Alembic pharma, vadodara, India. Hydroxypropyl methylcellulose K4M and K15M were gifted by Colorcon, Goa. Microcrystalline cellulose (Avicel PH 101), crospovidone, lactose, and Sodium starch glycolate were procured form Signet Chemical Corporation, Mumbai. PVP K30 was procured from S.D. Fine chemicals, Mumbai. All other excipients used were of an analytical grade, and procured from commercial sources.

Preparation of floating core tablet (trial batch):

Core tablets of bromhexine hydrochloride were prepared by wet granulation method. Accurately weighed 18 mg (calculation described by Robison and Eriksen[7]) of bromhexine hydrochloride was taken for preparation of core tablets. All other ingredients were weighed accurately and mixed in a glass mortar except talc and magnesium stearate. Add IPA slowly to the mixture to form a wet mass. Pass this mass from 20 number of sieve and place these granules for drying in oven. Set 60^{o}C temperature of oven for drying. After drying of granules, add require quantity of talc and magnesium stearate and mix well. The quantity of granules for matrix core tablet was compressed using a rotary compression machine (Hardik engineering, India) equipped with 6 mm round punches [8]. Formulation of preliminary trial batches of the core tablets is show in **Tables 1**.

TABLE 1: COMPOSITIONS OF TRIAL BACHES OF CORE TABLETS

Ingredients	H1	H2	H3	H4	H5	H6	H7
Bromhexine hydrochloride	18	18	18	18	18	18	18
HPMC K4M	12	24	36	36	48	36	36
Sodium bicarbonate	15	15	15	15	15	15	15
Citric acid	8	8	8	3	3	3	3
MCC	64	52	40	45	33	22.5	0
Lactose	0	0	0	0	0	22.5	45
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

* Talc and magnesium stearate was taken in quantity of 1 mg and 2 mg, repectively

Evaluation of prepared floating core tablet:

Weight variation: The prepared tablets were evaluated for weight variation to find out weight uniformity. Twenty tablets randomly taken from all the bathes and they were weighed accurately on electronic balance (Sartorius weighing India Pvt. Ltd, New Delhi*).*

Hardness and Friability: Hardness represents mechanical strength of tablets. Hardness of the tablets determined using Monsanto hardness tester (Janki impex Pvt. Ltd., Ahmedabad). The friability of prepared tablets was performed using roach friability apparatus (Electrolab, India). Ten tablets were selected and weighed before and after rotating in friability apparatus.

Floating behaviour of tablet in 0.1N HCl:

The floating behaviour of prepared tablet was studied in 0.1N HCl solution. The prepared tablets

were floated or not, were checked in 0.1N HCl solution. The floating lag time was determined in 0.1N HCl after placing the tablet in 0.1N HCl solution in 250 ml beaker [9].

Preparation of dual release core compressed tablets (trial batches for coat layer):

The core tablets of bromhexine hydrochloride were prepared by above procedure. The coat layer was prepared using disintegrants by direct compression method. Accurately weighted all ingredients were mixed in mortar. The die of the tablet machine was filled manually with the weighed amounts of the quick release part and the core tablet before the compression. Half quantity of fast releasing powder was place into the die cavity to make a powder bed; on the center of bed core tablet was placed. Then the remaining half portion of the powder was placed over the core tablet. The different formulations containing polymers in various concentrations are show in **Table 2**. Core Compressed tablet systems were prepared using a 12-mm diameter punch [10].

TABLE 2: TRIAL FORMULATION FOR COAT LAYER CONTAINING AZITHROMYCIN

Ingredients	C1	C2	C3	C4	C5	C6
Azithromycin	500	500	500	500	500	500
Crospovidone	15	30	45	-	-	-
Sodium starch glycolate	-	-	-	15	30	45
PVP K30	15	15	15	15	15	15
Avicel PH 101	80	65	50	80	65	50

* Talc and magnesium stearate was taken in quantity of 10 mg for each

Evaluation of dual release core compressed tablets: [11]

The dual release core compressed tablets were characterized for weight variation, hardness, friability, disintegration time, and floating lag time. The disintegration study was carried out using disintegration test apparatus containing 0.1N HCl. Time was noted in second for disintegration of outer layer of core-compressed tablets. The floating lag time was determined by placing tablet in 0.1N HCl solution and determines time to float the tablet on surface.

Preparation of dual release core compressed tablets:

The core compressed tablets of bromhexine hydrochloride and azithromycin were prepared using above procedure. The concentration of HPMC K4M and HPMC K15M were taken 25%, 30% and 35% individualy for preparation of core tablets. The wet granulation method was utilised for preparation of core tablets of bromhexine hydrochloride. The coat layer was formulated on core tablet using optimised C3 bach. The quantity of all ingredients are show in **Table 3**.

TABLE 3: FORMULATION OF DUAL RELEASE CORE COMPRESSED TABLET (CORE TABLET)

Ingredients (mg)	B1	B2	B3	B4	B5	B6
Bromhexine hydrochloride	18	18	18	18	18	18
HPMC K4M	30	36	42	-	-	-
HPMC K15M	-	-	-	30	36	42
Sodium bicarbonate	15	15	15	15	15	15
Citric acid	3	3	3	3	3	3
Lactose	51	45	39	51	45	39
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

* Talc and magnesium stearate was taken in quantity of 1 mg and 2 mg, repectively

Evaluation of prepared dual release core compressed tablets:

The prepared dual release core compressed tablets of bromhexine hydrochloride and azithromycin were evaluated for weight variation, hardness, friability and disintegration test using above procedure.

Drug content study (assay):

Ten tablets were taken and finely powdered in mortar. An equivalent amount to 18 mg of bromhexine hydrochloride was accurately weighed and transfer to a 100 mL volumetric flask; 70 mL of 0.1 N HCl was then added. The flask was shaken for 10 min. Finally, the volume was made up to the

mark with 0.1 N HCl. The mixture was then filtered and measured by high-performance liquid chromatography (LC-2010 CHT), Shimadzu, Japan. The method to quantify bromhexine hydrochloride and azithromycin was done by HPLC with C18 column (250×4.6 mm) having five µm particle size. The mobile phase consisted of an Acetonitrile: Phosphate buffer pH 6 in the ratio of 45: 55. The liquid flow rate of HPLC was 1 ml/min. The wavelength of detection was 215 nm.

Floating behavior study of prepared tablets:
The floating behaviour of prepared tablet was studied in 0.1N HCl solution. The prepared core compressed tablets were placed in 0.1N HCl containing 250 ml beaker. The floating lag time was determined by placing tablet in beaker, to float tablet on surface of 0.1N HCl solution containing beaker. The photograph shows the behaviour of tablet in beaker (**Fig.1**). The total floating time determine to check the tablet up to how much time tablet float on surface.

***In-vitro* drug release studies:** [12]
The in vitro dissolution studies were carried out using USP 6 dissolution apparatus type II (paddle method) at 100 rpm. Dissolution test was carried out for a total period of 12 h using 0.1N HCl (pH 1.2) solution (900 ml) as dissolution medium at 37 ±0.5°C. Five millilitres of the sample was withdrawn at regular intervals and replaced with the same volume pre warmed (37 ± 0.5°) fresh dissolution medium.

The samples withdrawn were filtered through 0.45 µ membrane filter, and drug content in each sample was analysed by high-performance liquid chromatography (LC-2010 CHT), Shimadzu, Japan. The wavelength of detection was 215 nm. The release of both drugs was determined simultaneously.

Mechanism of drug release from core tablets: [13]
Drug release mechanisms and kinetics are two important characteristics of delivery system in the dissolution system. The mechanism of drug release from prepared tablets was carried out by applying mathematical models. The data were taken from dissolution of bromhexine hydrochloride from core tablets.

Zero order: In zero order release study, percentage drug release versus time graph is plotted.

$$f_t = K_0 t$$

Where, f_t is fraction of dose release at time t. K_0 is zero order rate constant expressed in units of concentration/time.

First order: In first order release study, log percent drug remaining versus time graph is plotted.

$$\text{Log } Q_t = \text{Log } Q_o - Kt/2.303$$

Where, Q_0 is the drug amounts remaining to be released at zero hour. K is the first-order constant. Q_t is the drug amounts remaining to be released at time t.

Higuchi's model:
In Higuchi's model, percentage of drug released versus square root of time graph is plotted.

$$f_t = K_H t^{½}$$

Where, f_t is fraction of dose release at time t. K_H is the constant for higuchi‘s model.

Korsmeyer–Peppas model:

$$M_t / M_\infty = K\, t^n$$

Where, M_t / M_∞ is fraction of drug released at time t. K is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms. The value of n is given in **Table 4** for characterize of release mechanism.

TABLE 4: VARIOUS DRUG TRANSPORT MECHANISMS

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.45 < n = 0.89	Non –Fickian transport
0.89	Case II trasport
Higher than 0.89	Super Case II trasport

Comparison of dissolution profile of optimized batch with marketed formulation:
The dissolution study of conventional marketed formulation containing 8 mg of bromhexine hydrochloride carried out using same procedure as mention above. The comparison of dissolution profile done with optimised batch.

RESULT AND DISSCUSION:

Evaluation of prepared floating core tablets:

The evaluation parameters of prepared core tablets of bromhexine hydrochloride are show in **Table 5**. The weight variation of prepared tablets was found between 116.8 to 123.4, which is acceptable in range as per standard limit. Hardness and Friability data shows that good mechanical properties because the hardness of tablets were found near to 5- 6 kg/cm^2 and friability were found to less than 1%. Tablets from batch H1 were not floated properly due to less amount of HPMC K4M. Tablets from batches H2 and H5 moved up and down in solution due to unadequate quantity of HPMC K4M. Tablets from batches H3, H4 and H6 floated on surface of 0.1N HCl but brusting effect were observed may be due to microcrystalline cellulose (MCC). Tablets from H7 batch floated on surface of 0.1N HCl containing lactose instead of MCC. Batch H7 containing HPMC K4M in 30% concetration to tablet weight. The floating lag time was found to 69 seconds.

TABLE 5: EVALUATION OF FLOATING CORE TABLETS OF BROMHEXINE HYDROCHLORIDE (TRIAL BATCHES)

Evaluation Parameter	H1	H2	H3	H4	H5	H6	H7
Weight variation	119.2 ±4.3	117.5 ±5.8	123.4 ±2.9	120.8 ±5.7	117.7 ±5.2	121.7 ±4.2	116.8 ±3.6
Friability (%)	0.37	0.32	0.24	0.65	0.76	0.59	0.48
Hardness (kg/cm^2)	5.5	6.0	5	5.5	5	6	5.5
Behave of tablet in 0.1N HCl	Do not float up to 10 min	Float but move up & down	Float and slide burst tablet	Float and slide burst tablet	Float but move up & down	Float but burst tablet	Float tablet
Floating lag time (sec)	-	-	103	90	-	86	69

Evaluation of prepared dual release core compressed tablets (trial batches):

The paepared tablets were evaluated for different parameters which show in **Table 6.** The weight variation of all prepared batches found to be acceptable in range. The weight of all tablets were found between 742.2 mg to 762.6 mg. Friability of all batches was found to less than 1%, which show acceptable as per limit. Form hardness it can be conclude that the tablets show adequate mechanical strength because it was found near to 4.5 kg/cm^2. The disintegration time of outer coat layer were found between 63 to 90 seconds. Batches C1 to C3 containing crospovidone show less disintegration time compared to C4 to C6 containing sodium starch glycolate. As the concentration of disintegrants is increse the disintegration time decreases. Floating lag time of core tablets were found between 76 to 105 seconds.

TABLE 6: EVALUATION OF PREPARED CORE COMPRESSED TABLETS (TRIAL BATCHES)

Parameter	C1	C2	C3	C4	C5	C6
Weight variation	742.2±7.3	743.4±5.8	754.9±6.9	742.8±5.7	762.6±5.6	755.7±4.2
Friability (%)	0.68	0.82	0.57	0.65	0.69	0.83
Hardness (kg/cm^2)	4	4.5	4	5	4	4.5
Disintegration time of coat tablet (sec)	92	67	63	90	75	69
Floating lag time of core tablet (sec)	105	79	76	100	88	92

Evaluation of dual release core compressed tablets of bromhexine hydrochloride and azithromycin:

The evaluation of paepared tablets is show in **Table 7**. The weight variation of all prepared batches found to be acceptable in range. The weight of all tablets were found between 734.7 mg to 765.8 mg. The friability of all batches was found to be acceptable in range, less than 1%. Form hardness it can be conclude that the tablets show adequate mechanical strength because it was found near to 4.5 kg/cm^2. The disintegration time of outer coat layer were found between 65 to 73 seconds for all batches B1 to B6.

TABLE 7: EVALUATION OF DUAL RELEASE CORE COMPRESSED TABLET

Evaluation Parameter	B1	B2	B3	B4	B5	B6
Weight variation (mg)	734.7± 8.6	750.5± 4.8	753.4± 6.9	765.8± 3.9	745.8± 9.6	736.7± 4.2
Friability (%)	0.52	0.83	0.57	0.69	0.61	0.48
Hardness (kg/cm^2)	5	4.5	4.5	4	5	5
Assay of bromhexine HCl (%)	95.7	98.6	100.1	95.4	100.5	98.9
Assay of Azithromycin (%)	102.1	98.6	96.8	104.0	98.4	100.8
Disintegration time of coat layer (sec)	72	67	68	73	65	69
Floating lag time (sec)	94	85	87	100	83	81
Total floating time (hr)	>24	>24	>24	>24	>24	>24

Drug content study: The drug content for bromhexine hydrochloride was found between 95.7 to 100.1 % which is acceptable limit. The drug content for azithromycin was found between 96.8 to 104.0 % show acceptable in limit. From the drug content study it is concluded that content uniformity found in all batches.

Floating behavior of core tablets: The floating study of prepared tablets were carried out in 0.1 N HCl containg beaker. **Fig. 1** show the behavior of tablets with specific time. The floating lag time of all batches were found between 81 to 100 seconds. The lowest floating time was obsered in batch B6 containing 35% of HPMC K15M. total floating time of all the batches were found more than 24 hours which indicate that the prepared core tablet can float for suficient time in stomach.

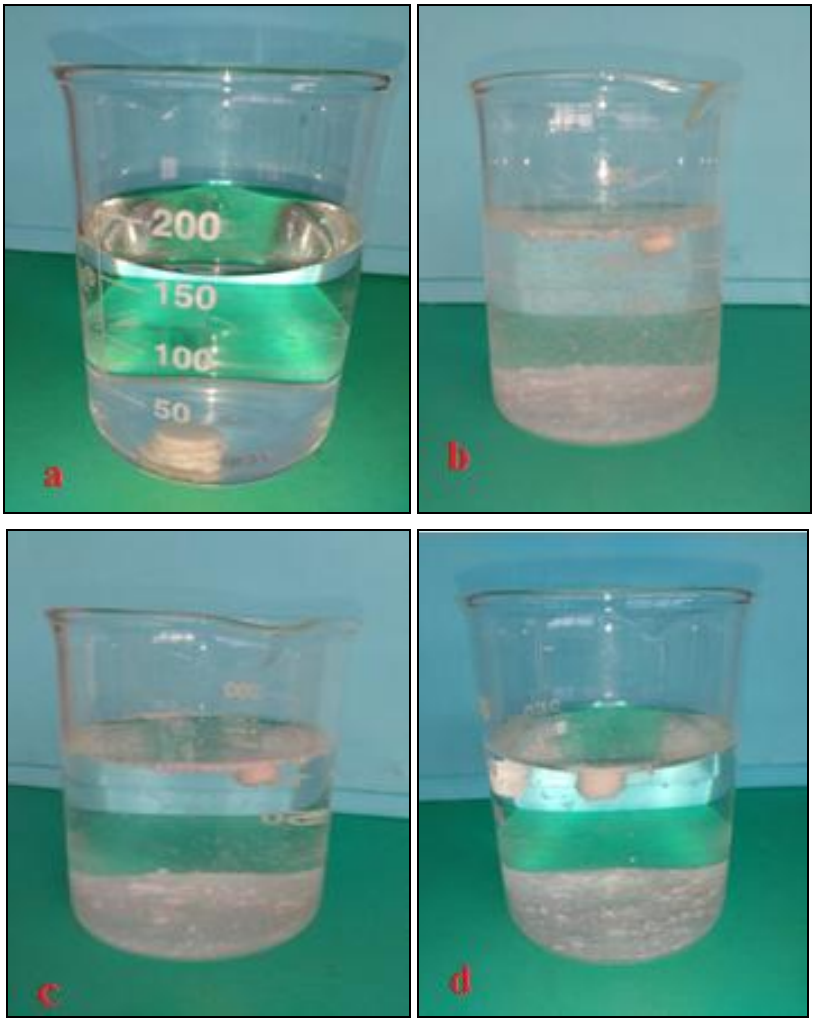

FIG. 1: FLOATING BEHAVIOUR OF CORE COMPRESSED TABLET AT DIFFERENT TIME a) AT 15 SECONDS b) AT 90 SECONDS c) AT 2 HOURS AND d) AT 10 HOURS

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

The drug relese of azithromycin and bromhexine hydrochloride from prepared dual release core compreesed tablet are show in **Fig.2** and **3**. The azithromycin was released about 80 % at 15 min. which shows the quick drug release. The bromhexine hydrochloride was released from prepared core matrix of HPMC K4M or K15M. The dissolution study were carried out up to 12 hr. As the concentration of HPMC K4M or K15M increases than the release of ambroxol hydrochloride from core tablets is decreses. Gradualy drug release of bromhexine hydrochloride was decrese as HPMC concentration icrease. Around 95 % of drug released at 8 hr in batches B1 and B2. In batch B6 slow drug release 95 % was found at 12 hr. In batch B5 containing 30% of HPMC K15M found adequate drug release of bromhexine hydrochloride.

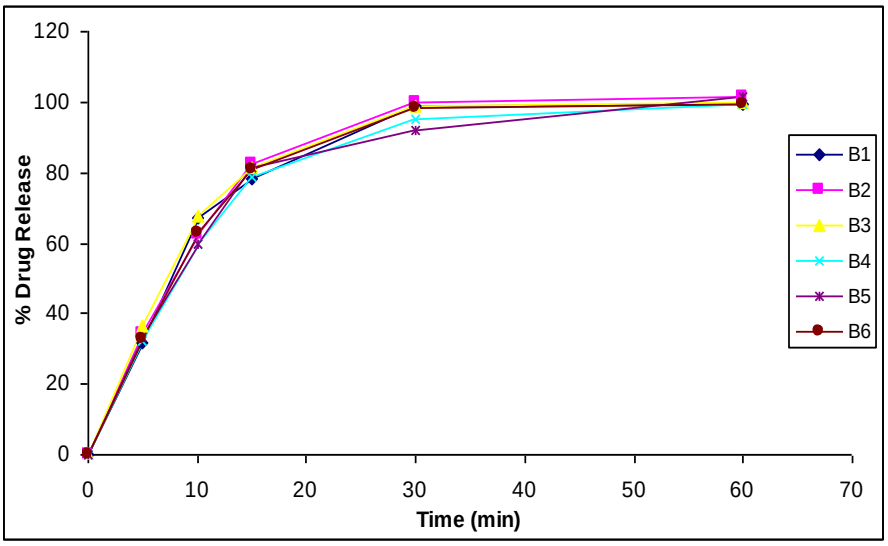

FIG.2: *IN-VITRO* DRUG RELEASE OF AZITHROMYCIN FROM CORE COMPRESSED TABLETS

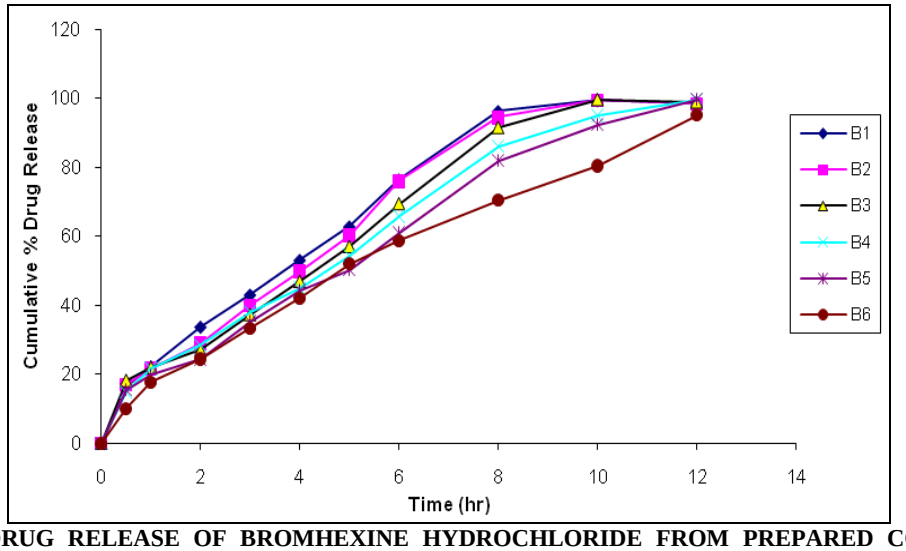

FIG. 3: *IN VITRO* DRUG RELEASE OF BROMHEXINE HYDROCHLORIDE FROM PREPARED CORE COMPRESSED TABLETS

Kinetic modeling of drug release:

The coefficient (R^2) was calculated for all batches using MS-excel and graphs were plotted. The value of rate constant and coefficient are show in **Table 8**. Based upon the regression coefficient, zero order drug release of bromhexine hydrochloride from prepared core tablets was observed. The drug release also follows the higuchi model. The drug release exponent was found to be 0.60 to 0.69 in korsmeyer peppas plot which indicated that the drug transport system is non –fickian type due to HPMC.

TABLE 8: RELEASE KINETIC MODELS FOR DUAL RELEASE CORE COMPRESSED TABLETS

Batches	Zero order	First order	Higuchi	Kosmeyar peppas	
		R^2 value		R^2 value	n value
B1	0.9307	0.8840	0.9684	0.9861	0.62
B2	0.9378	0.8773	0.9606	0.9703	0.62
B3	0.9573	0.8343	0.9560	0.9527	0.60
B4	0.9765	0.8356	0.9733	0.9828	0.63
B5	0.9863	0.7971	0.9659	0.9914	0.63
B6	0.9870	0.8990	0.9870	0.9951	0.69

Comparison of dissolution profile:

The comparison of dissolution profile of bromhexine HCl is show in **Fig. 4.** The dissolution profile of optimised batch was found non-identical with the marketed formulation. The drug release from marketed conventional tablet was found fast than dual release tablets. Almost drug was released at 60 minutes where as only 20 % drug released from prepared dual release tablets.

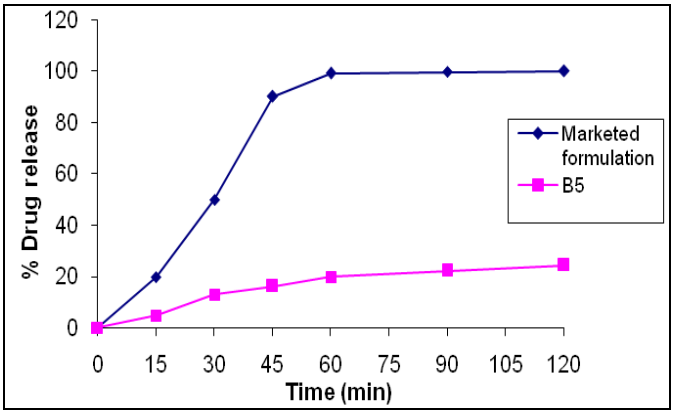

FIG. 4: COMPARISON OF DISSOLUTION PROFILE OF BROMHEXINE HCL OF OPTIMISED BATCH WITH MARKETED FORMULATION

CONCLUSION: The dual release formulation of azithromycin and bromhexine hydrochloride can successfully formulate by using core compressed tablet approach. Quick release of azithromycin was achieved using disintegrants. Floating core tablet was prepared for drug release in stomach because bromhexine hydrochloride is soluble in acidic pH. The HPMC K4M and K15M were used for floating approach with gas forming agents. The sustained release of bromhexine hydrochloride was accomplished using matrix formulation with HPMC K4M and K15M. The drug release of bromhexine hydrochloride achieved up to 12 hr. The prepared dual release core compressed tablets of bromhexine hydrochloride and azithromycin shows acceptable after evaluated for various parameters.

ACKNOWLEDGMENT: We thank Orex Pharma Pvt Ltd, Thane, India for providing the bromhexine hydrochloride as a gift sample.

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How to cite this article:
Patel BP and Patel DM: Design of Core Compressed Tablets of Azithromycin and Bromhexine Hydrochloride as Dual Release System. Int J Pharm Sci Res 2016; 7(10): 4055-63.doi: 10.13040/IJPSR.0975-8232.7(10).4055-63.