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DESIGN AND *INVITRO* EVALUATION AND COMPARISON OF HPβCD AND β CD COMPLEXED ALBENDAZOLE JELLY

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ABSTRACT

A high dosage of albendazole (ABZ) is required for treating systemic helminthe infections because of its low solubility. Aiming at increasing ABZ solubility, complexation with beta-cyclodextrin (β-CD)and hydroxyl propyl beta cyclodextrin(HP βCD).In this research work ABZ is complexed with cyclodextrins and oral jellies are formulated and comparison was done .One of the benefit of this formulation is these prepared jellies are increased bioavailability by-passing first pass metabolism. Difficulty in swallowing (dysphagia) is common among all groups, especially in elderly and pediatrics. Jelling agent is dispersed in water and jellies were prepared and jellies were evaluated for physical characteristics such as pH,in vitro % drug release, content uniformity, spreadability, viscosity, IR spectral analysis, syneresis .In vitro dissolution was carried out using the paddle method.

KEYWORDS: Jelly, Dysphagia, Albendazole, *In vitro* dissolution studies, HP βCD, βCD.

INTRODUCTION

Jellies are transparent or translucent semisolid preparations meant for external and internal applications. Usually jellies are prepared from natural gums such as pectin, sodium alginate or from synthetic derivatives of natural substance such as methyl cellulose, and sodium carboxy methyl cellulose.[1] ABZ is teratogenic and embryo toxic and cannot be administered to pregnant women. When used in lengthy therapies such as neurocysticercosis, ABZ can cause gastro intestinal pain, headaches, fever, fatigue, hair loss, thrombocytopenia, and liver degeneration. Hence hepatic patients are not recommended with ABZ treatment. The low cost and broad spectrum activity of ABZ make it typically the drug of choice for these cases .But the major disadvantage ABZ is its low solubility results in low absorbance through the GI tract and using ABZ for the systemic diseases can cause GI disturbance and detrimental side effects.[2] Therefore complexing with cyclodextrins could increase bioavailability. Despite its efficacy, the clinical usefulness of ABZ hampered by its poor oral bioavailability. ABZ has a very low water solubility, allowing its preparation only as suspensions. This suspension formulation has poor gastrointestinal absorption and displays high inter individual variation in absorption and elimination. ABZ is a basic drug with pKa value of 2.8 and 10.28, and in acidic medium it will remain in its ionized form, ABZ is poorly soluble and its aqueous solubility and it has weak basic properties and albendazole falls into the BCS class II category as has high permeability and low solubility. Because of its low aqueous solubility it is poorly and erratically absorbed following oral administration. Hetrocyclic and aromatic rings in the chemical structure of ABZ make it an ideal candidate for complexation with CDs.[3] CDs are cyclic oligosaccharides composed of α-1-4 linked glucose units which are used to increase the solubility, safety and stability of compounds. CD s form inclusion complex with drugs by taking up the drug molecule into their lipophilic inner cavity. Commonly used CDs are α,β and γ CDs, consisting of six, seven ,and eight glucopyranose residues. Hydroxy propyl beta cyclodextrin is a derivative of β CD with improved water solubility and safety, compared with its parent compound. The patients with dysphagia can be choked by water while consuming liquid formulations which can be eliminated by administering liquid formulation with high viscosity.[4] The gel dosage form overcome the disadvantages of both liquid and solid dosage forms and aim of this work is to improve patient compliance by development of jelly formulation and in this study complexing drug with β CD and HP βCD and oral jellies are formulated and comparison is done between cyclodextrins.

MATERIALS AND METHODS

Materials: Albendazole which is obtained as gift sample from Cipla Ltd, Mumbai and hydroxyl propyl beta cyclodextrin and beta cyclodextrin from Yarrow Chem. Products, Mumbai. And all other chemicals used in this study are of analytical reagent grade.

Formulation of Dru-Cyclodextrin Inclusion Complex[3]

Preparation of binary mixture of Albendazole /Hydroxyl propyl ß cyclodextrin and beta cyclodextrin: Various techniques for the preparation of drug-cyclodextrin complexes include co-precipitation, slurry complexation (kneading method), damp mixing, paste complexation, heating, dry mixing, neutralization, freeze drying, and slugging methods. In this work kneading method is used for the preparation of binary mixture; ABZ-HPβCD and ABZ-βCD.

Complexation with Hydroxyl propyl ß cyclodextrin and ß cyclodextrin by kneading technique

Method: The ABZ, β CD and HPβCD were prepared by kneading method, and the ratio Albendazole, hydroxyl propyl β cyclodextrin and beta cyclodextrin (1:0.5, 1:1, and 1:1.5) were prepared. In this method homogenous mass of drug and cyclodextrins were prepared by taking samples in a mortar and water was added and the mixture was ground for one hour and water was approximately added to maintain suitable consistency. The paste was dried in hot air oven at 40℃ for 48hours.The dried complex was further passed through 60#mesh and packed in closed container.

Characterization of binary mixture of ABZ-HPβCD

Fourier transforms infrared (FTIR) spectroscopy[3]

Fourier transform IR spectra were recorded for albendazole, HPβCD, and kneaded mixture. Samples were prepared in KBr disc (2mg sample in 200mg KBr).The scanning range was 400-4000cm^{-1}, resolution was 4cm.$^{-1}$Any change in the chemical composition after combining with the excipient were investigated with IR spectral analysis.

Formulation and Evalution of Oral Medicated Jellies[2, 5]

Preparation of oral medicated jellies

All the formulations were prepared using freshly boiled and cooled distilled water as per composition given in table 1.Syrupy base was prepared in a copper vessel dissolving the required amount of sugar in water on heating and stirring at 80 ˚c for about 90 min. All the required ingredients of the formulations were weighed accurately at different concentrations were dispersed in 50 ml of distilled water maintained at 95˚c.The dispersion was stirred at 95 ˚c for 20 min using magnetic stirrer to facilitate hydration of gums. The required amount of syrupy base was added to the gelling agent, with continuous stirring and the temperature is maintained at 80-85˚c.ABZ: HP βCD(same procedure is used for β CD)were added with stirring. The citric acid and methy paraben and propyl paraben were added by stirring. Propylene glycol was added as dispersing agent when the gelling agent used is sodium alginate. At last coloring and flouring agent were added. Finally the weight of the gel was adjusted to 100 gm with distilled water. The mixture was allowed to cool to form jelly and wrapped in to the gelatin paper and store in dry place. And the composition of various jelly formulation is given in Table 1.

Table. 1: Comparison of different jelly formulations of ABZ:HPβcd & ABZ:βcd.

INGREDIENTS	F1	F2	F3	F4	F5	F6
Albendazole (mg)	400	400	400	400	400	400
Guar Gum	2%	2%	2%			
Sodium Alginate				2%	2%	1%
HPβCD (mg)	200	400	600			
βcd (mg)				200	400	600
Methyl Paraben (mg)	100	100	100	100	100	100
Propyl Paraben (mg)	100	100	100	100	100	100
Sucrose (gm)	35	35	35	35	35	35
Citric acid (mg)	100	100	100	100	100	100
Colouring agent (mg)	q.s	q.s	q.s	q.s	q.s	q.s
Flavouring agent (mg)	q.s	q.s	q.s	q.s	q.s	q.s
water upto	100	100	100	100	100	100

Evaluation of Abz Oral Jellies[5, 6, 7]

Preformulation studies: The pre formulation studies were carried out for ABZ, β CD and HP βCD. Melting point, solubility, drug-excipient compatibility and FTIR spectral analysis was carried out.

Physical Appearances: The prepared jellies were observed visually for clarity, odor, texture and presence of any particle. Evaluation was done in terms of stick ness and grittiness by mild rubbing the gel between two fingers.

Determination of pH

The pH of the jelly was measured using Digital pH meter at room temperature. For this purpose 0.5 gm of jelly

was dispersed in 50 ml of distilled water to make 1% solution, and the pH was noted.

Viscosity

Viscosity of jellies was determined by an apparatus called Brookfield viscometer using spindle LV 4 at the rotation OF 3 rpm at room temperature. The jelly was squeezed out from the mold by making a cut of uniform size on the mold and viscosity is measured.

Syneresis

Syneresis is the contraction of the gel upon storage and separation of water from the gel. It is more pronounced in the gels, where lower concentration of gelling agent is employed. All the jellies were observed for signs of syneresis at room temperature (25 ˚c ± 5˚c) and 8˚c±1˚c.The formulations showing signs of syneresis were rejected and not considered for further studies.

Drug-Excipient Compatibility studies

The drug and the excipients were mixed in ratio of 1:1 and placed in borosilicate colored glass vials. These vials were sealed and placed in an oven maintained at 40˚c and 75%RH.The samples were observed after 15, 30 and 45 days for any color change or lump formation .FTIR spectra of the pure sample and cyclodextrins were measured by preparing dispersion in dry kBr using attenuated total reflectance FTIR spectrophotometer.

Spreadability

Spreadability of jellies was determined by an apparatus which consists of two wooden blocks provided with two glass slides. Lower slide fixed on a wooden block and upper slide with one end tired to a glass slide and the other end tied weighing the pan. About 2.5 gm of jelly was placed between two slides, and 1000gm weight was placed over it for 5 min to press the sample to a uniform thickness .80gm weight was added to the pan and the time in seconds required to separate the two slides was taken as a measure of spreadability. A shorter time interval to cover a distance of 7.5 cm considered as better spreadability and was calculated using the formula,

$$S=\frac{M \times L}{T}$$

***In vitro* drug release**

The in vitro drug release study of jellies is done using the paddle apparatus method. The dissolution test is carried out using the solution 0.1N HCL (900 ml) at 37±5˚c and RPM used is 100.From the dissolution apparatus a sample of 5 ml is withdrawn at a time intervals of 5,10,15,20,25,30 min and the withdrawn sample is replaced with fresh dissolution media.

Content Uniformity

The jellies were taken out of molds and weighed individually and the gel equivalent to 400 mg was taken in 100 ml volumetric flask dissolved and made up to the volume using 0.1 N HCL. The content uniformity was estimated by UV spectrophotometer at 249 nm If needed sample should be filtered using Whattmann filter pater.

Stability Study

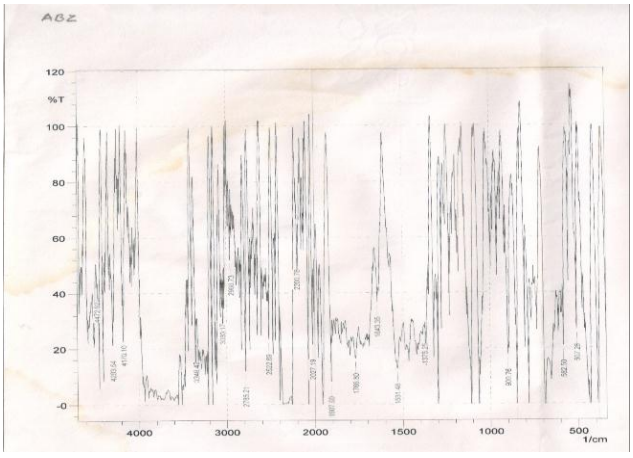
The main objective of stability study is to evaluate stability of optimized formulation at different temperature and humidity conditions. Optimized batch has been placed for 45 days at 40˚c ±2 ˚c and 0-8˚c. At the end of each week, the formulation were evaluated for viscosity, *in-vitro* release, and % drug content.

RESULTS AND DISSCUSSION

Characterization of binary mixture of ABZ-HPβCD

FTIR Spectroscopy

Drug-excipient compatibility studies were also confirmed by FTIR and the spectra of the drug(ABZ),HPβCD, and ABZ-HPβCD physical mixture are shown in figure 1.The FTIR studies from the spectra confirmed the absence of any chemical incompatibility between the drug and the hydroxyl propyl beta cyclodextrin. The spectrum of ABZ showed N-H stretching vibration at 3336 cm^{-1}, bending vibration at 1525-1630 cm^{-1} and aliphatic C-H at 2958 cm^{-1}, stretching of alkane at 2959 cm^{-1}, coo bending of ketone at 1710cm^{-1}.The spectrum of ABZ has NH stretching vibration at 3336 cm^{-1} due to carbamate. The spectrum of HPβCD is characterized by intense bands at 3,300-3500 cm^{-1}due to O-H stretching vibration. The vibrations of the ―CH and CH2 groups appears in the 2,800-3,000 cm^{-1} region, CH stretching at 1164.15 cm^{-1} and H-O-H bending at 1647 cm^{-1}.The kneaded mixture showed superimposed spectra of ABZ and HPβCD which proves the compatibility of excipients with the ABZ.



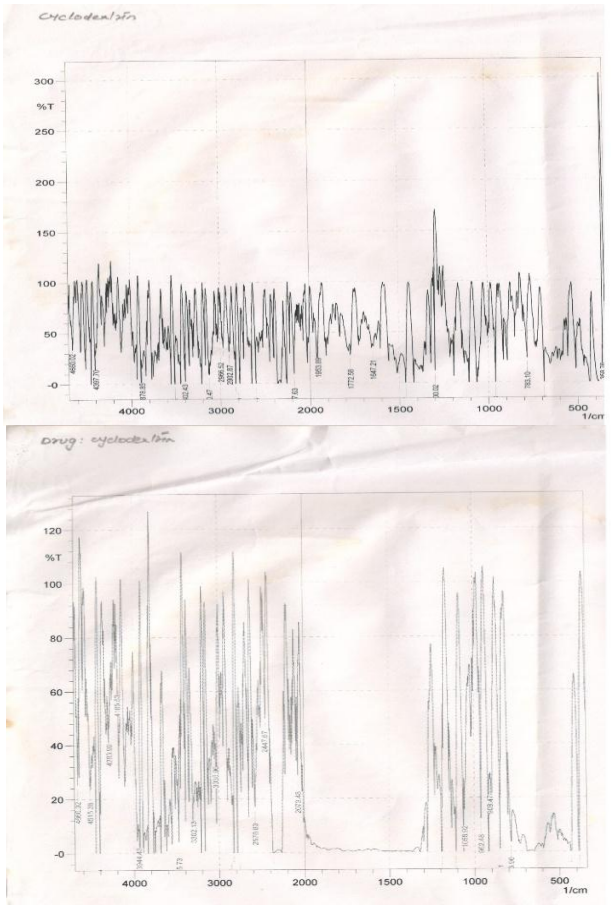


Fig. 1: FTIR Spectroscopy of ABZ, HPβCD, and ABZ: HPβCD.

Evaluation of Abz-HPBCD & Abz-βcd Jelly

From batch no F1, F2 and F3 was formulated employing drug, gelling agent and hydroxyl propyl β-cyclodextrin. And the ratio of drug :cyclodextrin is taken as1:0.5, 1:1, 1:1.5 whereas F4, F5 and F6 were formulated by employing drug, gelling agent and β-cyclodextrin and the ratio used is 1:0.5, 1:1, and 1:1.5 respectively. These formulations were evaluated for various quality parameters to determine their stability. Formulations F1 to F3 contain guar gum as the gelling agent. The formulations F4 to F6 contain sodium alginate as gelling agent.

General Appearance

Physical observation of jellies is important to justify the patient acceptance and compliance of the products. It is observed that parameters like appearance, texture, color and odor are acceptable for all formulations. All batches of soft gels were transparent in appearance. The gels of batch no 3 was non sticky and non-gritty while the gel of batch F1and F2 were sticky and gritty due to the higher concentration of guar gum, and F6 were found to be non-sticky and non-gritty and smooth in appearance and F4 andF5 were sticky may be due to higher concentration of sodium alginate. The physical evaluation is given in Table 2.

Table. 2: Physical Appearance of ABZ:HPβCD&ABZ:βCD.

Test parameter	F1	F2	F3	F4	F5	F6
Clarity	T	T	T	T	T	T
Consistency	A	A	A	A	A	A
Texture	S & G	S & G	NS & NG	S & G	S & G	NS & NG
T:Transparent, A:Acceptable, S:Sticky, G:Gritty, NS:Non sticky, NG:Non gritty						

Fig. 2: Oral jellies of ABZ complexed with HPβCD&βCD.

Visocity: The viscosity measurements supported visual inspection results. The viscosity of all batches were acceptable. The consistency and viscosity of the soft gels related to each other because both are dependent on concentration of gums used. Effect of co solute on the viscosity and consistency of all the batches of soft gels were same because the co solutes were used at same level in all the batches. It is clearly observed that change in viscosity and consistency of soft gels is influenced by gelling agent concentration. Evaluation of viscosity is given in table no.3 and in figure 3.

Table. 3: Viscosity of different jelly formulations of ABZ:HPβCD &ABZ:βCD.

Formulation Code	Viscosity (cps)
F1	60600±44
F2	59600±49
F3	56700±35
F4	62500±37
F5	64500±29
F6	55200±30

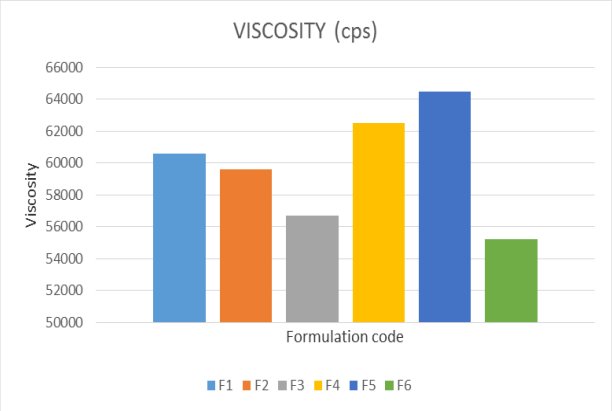


Fig. 3: Viscosity of different soft jelly batches F1 to F6.

Syneresis

Gels experience syneresis or de-swelling due to the release of liquid, resulting in shrinkage of gels and reduce quality. Syneresis is one of the major problem associated when lower concentration of gelling agent is used. It was observed after 24 hr of jelly preparation. At room temperature syneresis was not noticed, probably due to binding of free water by co-solute.F3 and F6 show very less degree of syneresis at room temperature and in refrigerator.(2-8 ˚c).

Percentage Drug Content

The drug content was found in the range of 95.6%±0.63% -98.2 %±0.63% for all the batches of ABZ, which is well within acceptable limits. Percentage drug content is given in table no 4 and in figure no 4.

Table. 4: Percentage drug content of different jelly formulations of ABZ:HPβCD &ABZ:βCD.

Formulation Code	% Drug Content
F1	96.5±0.33
F2	95.6±0.46
F3	98.2±0.66
F4	93±0.41
F5	95±0.36
F6	97±0.58

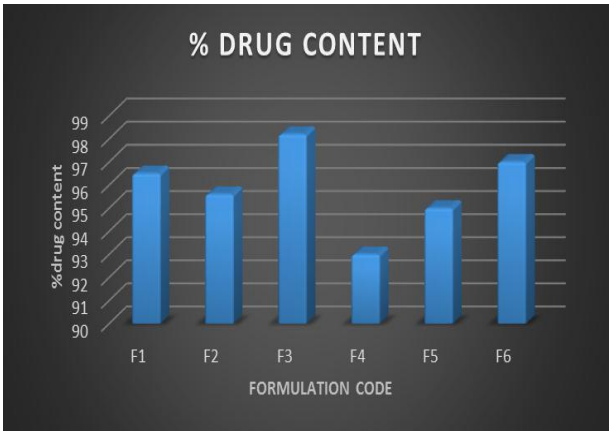


Fig. 4: % drug content of different soft jelly batches F1 to F6.

pH: The pH of all the jelly formulation is adjusted preferably to 4.0 or up to 7.0.This is because when pH is below 4 jelly preparation liable to cause syneresis and stability of the preparation deteriotes in some cases. When pH is 6 or close to neutrality the jelly preparation is far more excellent in stability. Therefore the pH of the formulated gels were adjusted and maintained in between 5 and 7 using citric acid as buffering agents,and is given in table no 5 and in figure no 5.

Table. 5: Viscosity of different jelly formulations of ABZ: HPβCD &ABZ: βCD.

Formulation Code	PH
F1	6.2±0.02
F2	6.4±0.04
F3	6.1±0.03
F4	6.2±0.04
F5	6.2±0.02
F6	6.3±0.03

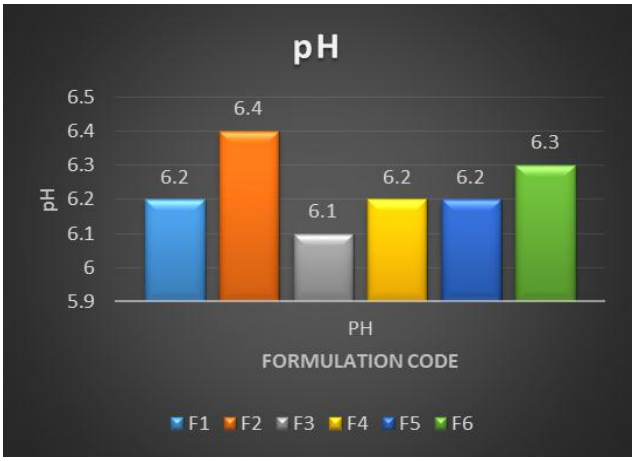


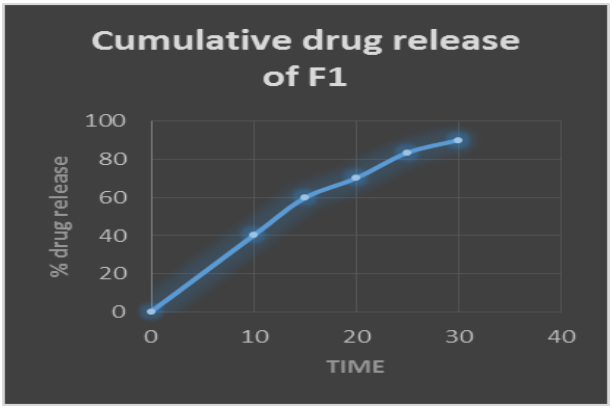
Fig. 5: pH of different soft jelly batches F1 to F6.

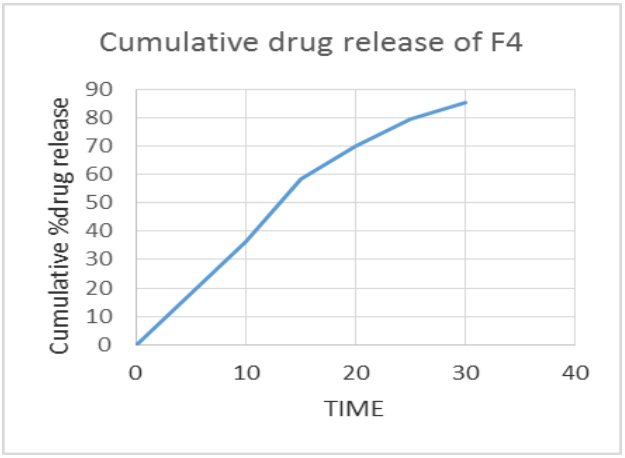
IN VITRO DISSOLUTION

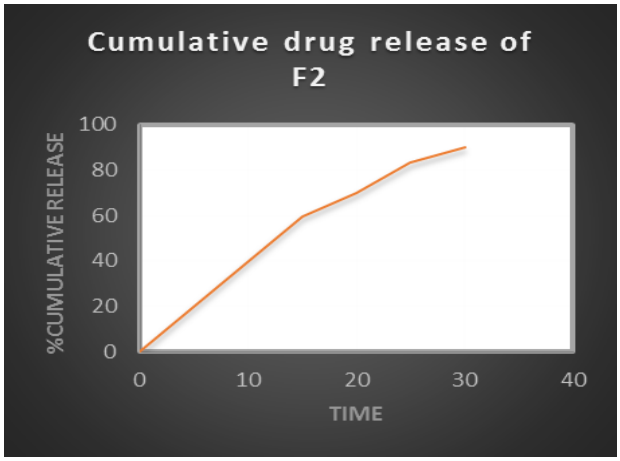
The results reveals that batch no F3 and F6 exhibited acceptable consistency and viscosity. And from the dissolution studies it is found that batch no F3 and F6 having about 90% to 95% drug release than compared to other batches. From the dissolution studies it is found that F3 (ABZ: HPβCD) have more drug release compared to other batches; and F3 is considered as optimized formulation. Percentage drug release is given in table no 6 and graphical representation is given in figure no 6.

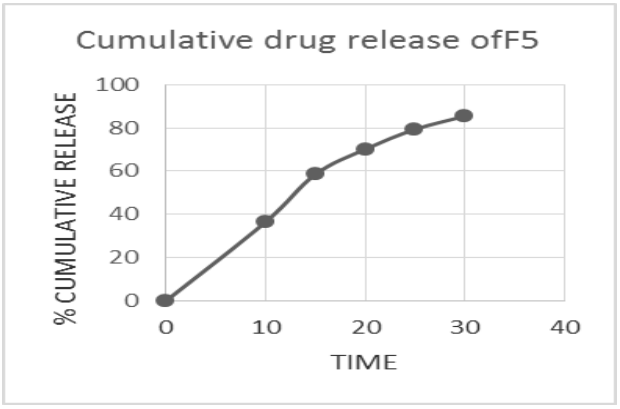
Table. 6: *In vitro* dissolution data of abz complexed jellies.

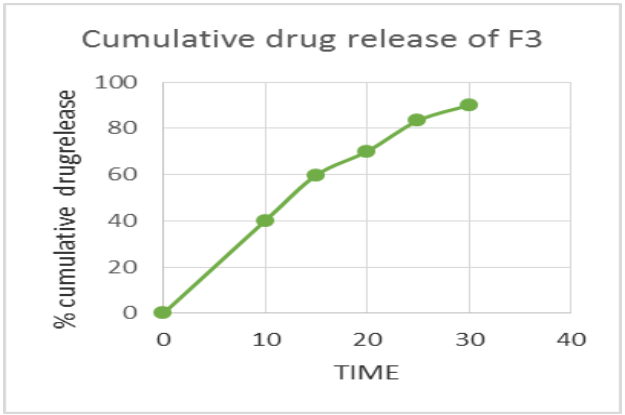
Time in minutes	Cumulative Percentage drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
10	34.11	35.31	46.11	36.5	37.1	40.12
15	48.91	47.75	60.01	58.55	63.1	59.76
20	65.7	70.12	76.41	70.15	73.21	70.11
25	73.52	74.5	85.85	79.35	81.55	83.44
30	85	88	92.1	85.41	89.1	90.1











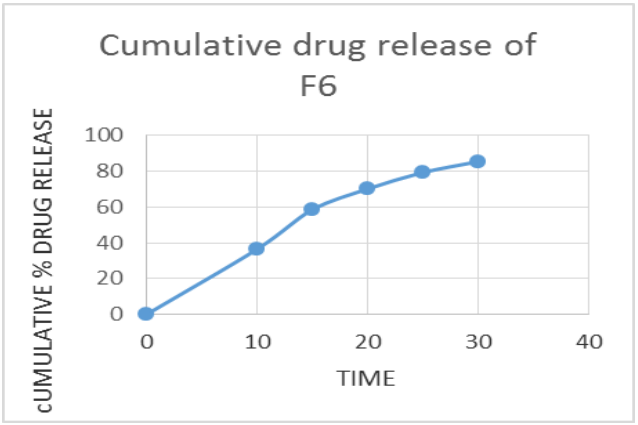


Fig. 6: Dissolution data of formulations F1 To F6.

Stability Study

The optimized formulation F5 were put on short term stability by packing in HDPE containers in stability chamber for 45 days at 40˚c ±2 ˚c and 0-8˚c.

Physical Parameters

The physical parameters of optimized jelly kept for stability study were evaluated and compared with the initial values for any significant changes. Results of which is shown in table 8**.**In the stability study done for 45 days it was noted that the surface was free of any kind of microbial or fungal growth or bad odour. No change in the appearance of jelly and it shows not less than 96% drug content, which shows that there are no significant changes in drug content. The results obtained from stability studies for 45 days showed that all physical parameters are within the specified limits and is given in table no.

Table. 6: Stability Evalution of Optimized Formulation.

Formulation Code	Temperature	Appearance	pH	Viscosity
F3	0-8 ˚c	SMOOTH	6.1	56700
	40±2˚c	SMOOTH	6.3	59600

4.4.2. Dissolution Study

Dissolution study was performed at the end of 7th day, 15thday, 30th day, 45th day and compared with the initial dissolution data for any significant changes, and it's given in figure 6. Based upon above stability study carried out for 45 days, it was concluded that the optimized formulations is stable and have same percentage of drug release, under ambient conditions.

CONCLUSION

This formulation can be effectively employed for oral delivery of poorly soluble ABZ complexing with cyclodextrin for pediatric, geriatric and dysphagia patients as alternative to solid dosage forms. Physical observation of jellies is important to justify the patient acceptance and compliance of the product. pH of all formulations are acceptable range. Drug content was found to be satisfactory. The formulations F1 to F3 were prepared by selecting different concentrations of HPβCD and F4 to F6 were prepared by selecting different concentration of βCD and from the results obtained it is found that F3 (ABZ: HPβCD, 400:1.5) and F6 (ABZ:βCD, 400:1.5) were optimized. From further stability studies and dissolution studies it was found that F3 formulation is having more percentage drug release compare to F6 and in terms of other parameters like viscosity and syneregsis.

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