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Preparation of Ibuprofen as Pediatric Candies

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Abstract

Purpose: to present model drug (Ibuprofen) as gelatine candies for paediatric use.

Methods: Bovine gelatine was used as the vehicle for the model drug ibuprofen. Compatibility of ibuprofen and gelatine was studied by UV and IR spectrophotometry and by kinetic study. The gelatine candies were prepared by dispersion of all ingredients in phosphate buffer pH 7.2 after optimization of concentration of gelatine and other additives, then poured in Teflon moulds, left to solidify at room temperature.

Candies were evaluated for drug content uniformity, drug release and efficiency of the preservative used (methyl paraben). Preliminary stability study at 40^{o}C and 75% relative humidity (RH) was also done for three months .

Ten kids age (4-7) years participated in the evaluation of taste, consistency and handling ability using "faces scale" and according to the regulations of Jordanian FDA.

Results: this study showed good compatibility of IB with gelatine, fast and almost complete release of and high efficiency of preservative used.

The prepared candies were found stable at 40^{o}C, 75%RH for three months. Results also showed high rate of acceptance of this medicated candies by kids.

Conclusion: Edible gelatine candies can be used to deliver ibuprofen to kids successfully.

Key words: *gelatine, ibuprofen, paediatric formulation.*

Abbreviation : IB (ibuprofen), GL (gelatine), FDA(food and drug administration), RH (relative humidity)

1. INTRODUCTION

Safe and effective pharmacotherapy for paediatric patients requires the timely development of medicines and information on their proper use appropriate to the age, physiological condition and body size of the child. Formulations developed specifically for children are often needed.[1]

Paediatric practice requires a range of dosage forms that are acceptable at different ages and abilities and a range of strengths or concentrations allowing administration of the correct age-related dose. Seriously ill children will require intravenous drug administration and will prefer this to frequent intramuscular injections. For less serious illness and long-term administration the oral route will be preferred but other routes such as buccal, nasal, transdermal and rectal can be useful in some circumstances.[2]

Developing paediatric formulations is a very challenging subject, there are a lot of parameters that should be taken into account and there are still many open questions. Solid dosage form present some issues, as children have difficulty swallowing whole solid drug carrier like tablet or capsule. Moreover providing age-appropriate doses at different strengths is a big issue , while problems in dosing accuracy, stability, palatability and unknown bioavailability of compounded products exist in liquid forms.[3] However, The vast majority of paediatric formulation are for oral administration. McNally and Railkar state that 90% of paediatric formulation are for oral adminstarion.[4]

Gelatine is a mixture of protein and polypeptides products derived by hydrolysis of animal collagen, contained in bones and skins.[5] All reputable gelatin manufacturers today follow the Quality Management System according to ISO 9001. [6] For pharmaceutical grade gelatins, strict regulations from the Food and Drug Administration (FDA), the European regulation and European Pharmacopoeia must be met.[7] The safety of gelatine has been studied by many workers as an edible substances, no reported data about restriction of its use especially for kids are available. [8]

Ibuprofen is non steroidal antiinflamatory agent which is widely used for paediatrics as analgesic antipyretic and antiinflamatory in management of fever, pain and rheumatoid arthritis.[9] In this work an attempt to use gelatine edible candies as dosage form for paediatric use using ibuprofen as model drug.

2. MATERIALS AND METHODS

2.1 Materials

Bovine Gelatin was kindly given as gift from Zhuhai Ting Kai (China) Ibuprofen and methylparaben were given as gifts from Dar Al-Dawa in Amman(Jordan) , glycerol, different colorants, flavours (of Rimon Chemicals Est, Germany), sucrose were all given as gifts by HIKMA pharmaceuticals in Amman(Jordan).

2.2 Methods

2.2.1 Spectrophotometric analysis of Ibuprofen (IB) and Gelatine (GL)

A sample of IB in phosphate buffer pH 7.2 was scanned using Ultaviolet-visible spectrophotometer : Jasco V530, Japan. The spectrum was in agreement with references.[10] A wavelength 262 nm was chosen to construct the calibration curve. This buffer was chosen because it will be used in preparation and dissolution study.

A stock solution of 0.1 % of IB in phosphate buffer pH 7.2 was prepared by dissolving the powder drug in pre-prepared buffer, sonication then filtration. Series of dilutions were prepared and U.V absorbance at 262 nm was

measured. The dilutions and measurements were repeated three times and average absorbance was calculated. A linear relation between absorbance and concentration following Beers Law was observed in concentrations between 50 – 250 mcg/ml.

U.V scanning of 1% GL solution in phosphate buffer pH 7.2 gave a small broad peak in the range 250-270 nm with absorbance = 0.1 at 262 nm. To study if the absorption is additive, series of solutions containing 0.25, 0.5 and 1% GL in phosphate buffer pH 7.2 were scanned and absorption at 262 nm was measured. Then solutions containing IB mixed with 0.25, 0.5 and 1% GL were prepared. All solutions were scanned and absorption at 262 nm was measured triple.

2.2.2 Compatibility of IB with Gelatine

Compatibility of IB with GL was studied by U.V and IR spectrometry and kinetic study using UV spectroscopy.

IR analysis

A sample of IB and GL was scanned each alone from 3500-400 cm^{-1} using KBr disc in Shumadzu Irprestige-21 . Then a sample of solid dispersion of IB in GL was scanned and results were interpreted. The solid dispersion was prepared using 1:1 weight mixture.

Kinetic Study

A solution of mixture of 1% GL and 0.1 % IB in phosphate buffer pH 7.2 was prepared and incubated at room temperature (in dark and light) and 40^{o}C. Samples were drawn on time schedule , proper dilutions were made and concentration of IB was measured by UV spectrophotomer at 262 nm.

2.2.3 Preparation of Placebo candies

Three concentrations of GL were tried to prepare the placebo candies as in table 1. Three formulas were prepared. The safety of all ingredients is approved by Food and Drug Administration.

The candies were prepared as follows: (100 ml dispersion)About 70 ml of phosphate buffer were placed in beaker on a magnetic stirrer with heater. The temperature was raised to 37-40 ^{o}C, and the stirrer was put on 50 rpm. Then the powdered gelatine was added gradually to avoid agglomeration. Stirring was continued for 10 minutes then other components were added gradually to the dispersion. The volume was then completed and stirring was continued for 20 minutes, during which the temperature and stirring speed were decreased gradually. The dispersion was then poured in teflon moulds each contained 10 ml and let to jellify at room temperature.

After 2-3 hours the candies were able to be removed from moulds easily (Figure 1) and put in a jar. Also unit polyvinyl moulds in which the candies could be kept but need cover package were tried.

Ten kids (6 males, 4 females, age 4-7) participated in testing these placebo candies in the criteria of taste, handlability, softness, mouth feeling and eligibility. The kids parents signed the required consents which was prepared according to Medical Studies Law of the Jordanian FDA.[11] A scale of four faces was used (figure2). According to the results, concentration of 6% GL (F2) was chosen to prepare the medicated candies.

Table 1: composition of placebo candies.

Composition	F1	F2	F3
Gelatine	5%	6%	7%
Glycerol (humectant and plasticizer)	1%	1%	1%
Sucrose (sweetener)	10%	10%	10%
colour	0.5%	0.5%	0.5%
flavour	0.5%	0.5%	0.5%
Phosphate buffer pH 7.2	To 100%W/V	To 100%W/V	To 100%W/V

Figure 1 : The prepared candies.

Figure 2: Four faces scale used to evaluate the candies.

2.2.4 Preparation of medicated candies (500 ml dispersion)

The medicated formulas were prepared from F2 by adding preservative (1 gm methylparaben or 0.2%) [12] as well as the IB (5 gm). The same procedure described in the preparation of placebo candies was followed with some modifications. About 50 ml of gelatine in buffer dispersion was transferred to small mortar and 5 gm of IB was added and dispersed by pestle thoroughly to avoid agglomeration. Then the content of the mortar was added gradually to the gelatine dispersion with continuous stirring and the volume was completed. The dispersion was then put in a water bath with controlled temperature in which the temperature was decreased gradually with continuous shaking. Just before the gelling point, the dispersion was poured in the moulds. Colouring agent was not added to prevent interference with analysis of the IB. Other batch named (F*) was prepared which contained IB and gelatine only to compare results of drug release and to ensure the non -interference of other components.

Each of the Teflon moulds used handles 10 ml exactly, so the unit dose of these medicated candies contained 100 mg of IB/dose unit.

2.2.5 Evaluation of the Medicated Candies

2.2.5.1 Drug Content

Being unit doses, the criteria of USP for IB tablets was followed to ensure uniform distribution of IB in the dispersion especially during cooling process. Drug content of medicated F2 was determined by gradually warming 20 unit doses until liquefied. A volume equivalent to 0.5 g IB was measured by measuring cylinder. Samples were drawn three times and diluted with the same buffer then measured by UV spectrophotometer at 262 nm. An average ± 5% was taken as accepted margin of variation. Then each unit dose was evaluated individually.

2.2.5.2 Softening time

Softening time was measured by taking 5 unit doses and put each in a beaker with stirrer in 5 ml of phosphate buffer pH 6.5 on 20 rpm and time for softening and disintegration of the unit candy was calculated as an average time in minutes ± SD.

2.2.5.3 Drug release and dissolution

The same criteria of USP 2009 for IB tablet were followed. Drug release study was carried out using dissolution rate test apparatus USP XXIII (Type II) (Erweka DT600,Germany). The dissolution medium used was 900ml of phosphate buffer pH 7.2 and the study conducted at 37^{o}C with 50 rpm. The sample was withdrawn at different time intervals and replaced with fresh medium in order to maintain sink condition. The withdrawn samples were diluted suitably and drug content was estimated using U.V-spectrophotometer at 262nm. Also the same test was conducted using 100 rpm stirring speed.

2.2.5.4 Taste evaluation

Using the same scale and same regulations for placebo, the medicated candies were tested. The same kids who had tested the placebo candies participated in this study after their parents had signed the consent that illustrated all details of the experiment. Here the kids did not swallow the candies, but only chewed them then washed their mouths thoroughly with normal saline. As a request of the regulation this test was performed under the supervision of a paediatrician. Handleability, softness, mouth feeling, eligibility and sweetness were all evaluated by the kids with the help of their mothers. Results were expressed as pie charts.

2.2.5.5 Preservative efficiency

Determination of preservative effectiveness (methyl paraben 0.2%) was done as described by Kamysz and Tureka with some modification [13].

Ten millilitres of medicated formula 2 were warmed to 38^{o}C to liquefy, then separately inoculated with proper volumes of suspension *Staphylococcus aureu*s , *Escherchia coli* and *Candida albicans* to achieve an approximate population of 10^5 cells per ml of the sample formula. The prepared samples were incubated at room temperature (18-25 ^{o}C) for 21 days.

At 6hr, 18 hr and 2 days, 7 days and 21 days after inoculation 0.1 ml of inoculated samples were transferred onto nutrient agar for bacteria and Sabourauds Dextrose agar for fungi. The inoculated nutrient agar plates were incubated at 37^{o}C for 48 hours and Sabourrauds Agar were kept at room temperature for 5 days. The total plate count was prepared to be performed. The same procedure was repeated with sample F2 without preservative as positive control.

2.2.5.6 Preliminary stability study

Preliminary stability study was done by incubating the medicated candies (Medicated F2) in polyethylene containers at 40^{o}C ±1 ^{o}C , 75% RH for 3 months. During this period samples were withdrawn let to jellify again at room temperature, and drug content as well as drug release was measured. Each time 3 samples were analysed and average drug amount ± SD was calculated.

3. Results And Discussion

3.1 Compatibility of IB and GL

3.1.1 UV Spectrophotometric analysis of Ibuprofen (IB) and Gelatine (GL)

Results of UV analysis of Gl and IB-GL mixture are presented in table 2 and 3. Gelatine has negligible UV absorption upon dilution to 0.5% and 0.25% and an additive absorption at 1% with different concentrations of IB.

Thus, when perform other tests, gelatine was diluted to these concentrations and less and the absorption was almost zero.

UV scanning of IB-GL mixture showed no additional peeks out of the range of 250-270 nm which supports the separate behaviour of the two substances in solution as shown in figure 3. The diluted gelatine –IB mixture gave the same absorption value of IB alone.

Table 2 : absorbance values of different gelatine concentrations in phosphate buffer 7.2 at 262 nm and room temp.

Conc. of GL	1%	0.5 %	0.25%
Absorbance at 262 nm	0.1 ± 0.001	0.0	0.0

Table 3: Absorbance values of IB and IB-GL solution mixture in phosphate buffer 7.2 at 262 nm and room temp.

Conc.	0.01% IB	0.01% IB + 1%GL	0.01% IB + 0.5%GL	0.01% IB + 0.25 %GL	0.025%IB	0.025%IB + 1%GL	0.025%IB + 0.5%GL	0.025%IB + 0.25%GL
Absorbance at 262 nm ± SD	0.14 ±0.001	0.24 ± 0.002	0.14 ± 0.002	0.14 ± 0.001	0.7 ± 0.010	0.8 ± 0.012	0.7 ± 0.002	0.7 ± 0.10

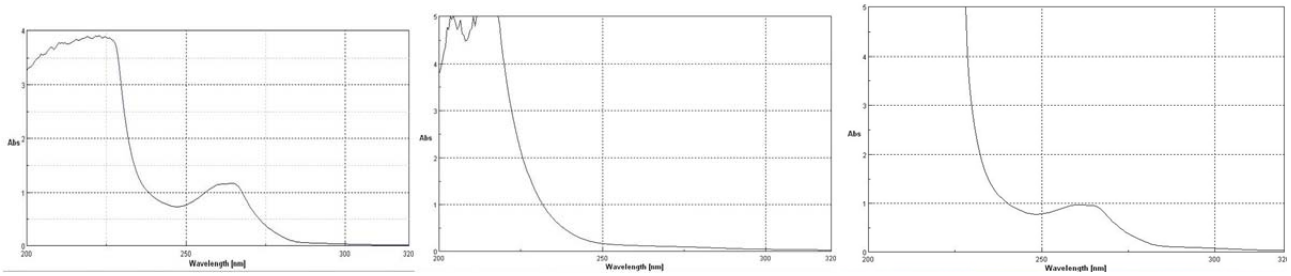

Figure 3 : UV scanning results of a) IB, b) GL and c) IB-GL mixture.

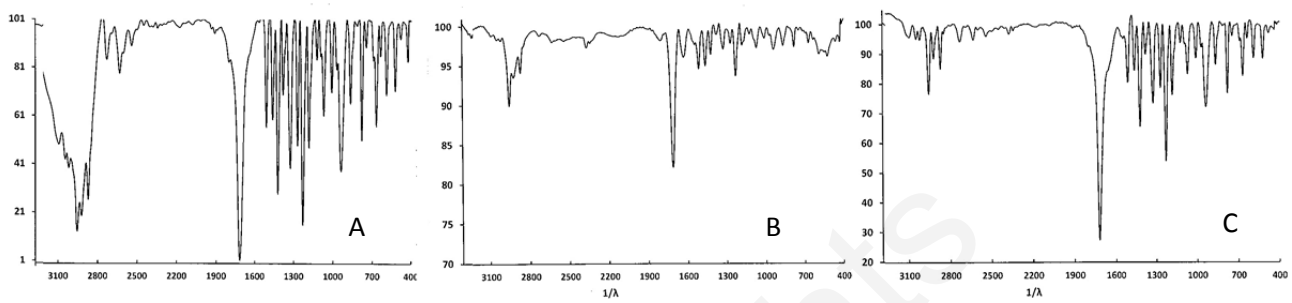

Figure 4: IR results of A): IB, B) GL and C) IB-GL solid dispersion

Table 4: Results of kinetic study of IB-GL solution mixture in phosphate buffer 7.2 at room temperature,40^{o}C under normal day light and in dark place

Percent total IB content	Zero time (base line)	2 days	10 days	2 weeks	4 weeks	8 weeks	12 weeks
Room temp, day light	100 ±1%	101 ± 0.5%	99 ± 0.3%	99.5 ±0.4%	100.2 ± 1 %	98.5 ±1.5 %	99.5 ±1% (with faint yellow color)
Room temp (dark place)	100 ± 0.5 %	99 ± 0.6%	100.5 ± 0.7%	99.6 ± 0.8 %	101 ± 1%	99.2 ±0.4%	99.5 ±0.7%
40^{o}C (incubator)	100 ± 0.5%	98.5 ± 0.7 %	100.2 ± 0.5%	99 ± 1%	100.3 ±0.6%	99.6 ±0.8%	99.5 ± 1%

3.1.2 IR spectroscopy analysis

Results of IR analysis of IB, GL and IB-GL mixture are presented in figure 4. The spectrum of IB-GL mixture (figure4 c) showed that there was neither appearance of new peaks nor disappearance of original peaks as compared with IB alone (figure 4 A) and GL alone (figure 4 B). This suggests that there was no incompatibility between IB and GL.

3.1.3 Kinetic study

Kinetic study showed stability of IB in IB-GL mixture at the conditions specified. Total drug content was obtained over 3 months of test and no rate constant was able to be calculated. Results are shown in table 4.

3.2 Evaluation of the medicated candies

3.2.1 Drug content, softening time and drug release and dissolution

Results of drug content analysis of unit candies reflected the efficiency of preparation method and uniformity of mixing process. All candies gave drug content between minimum value of 96% and a maximum value of 102% with a mean of 98.6% and standard deviation of 2.15%. The assay of twenty candies gave drug content of 98.1%

Softening time which reflects the effect of the saliva on candy in the mouth before swallowing was calculated as 4 ±0.8 minutes. However the candies can be sucked or chewed before swallowing.

Results of drug release are illustrated in table 5 and figure 5. The dissolution test showed an accepted drug releases of more the 80% of the drug in 30 minutes for all tested formulas (medicated F2 at 50 and 100 rpm and F*). A short lag time of few minutes was noticed, and then the drug started to release quickly. Medicated F2 and F* gave very similar release profile of IB. This suggests that excipients present in medicated F2 had no interference with IB release and analysis. While medicated F2 at stirring speed 100 rpm gave higher drug release in the first 30 minutes than drug release at 50 rpm stirring speed. Here, the stirring speed appeared to be the major factor that enhances drug release from medicated F2.

3.2.2 Taste evaluation

Evaluation of placebo candies showed that 8 out of the ten participant kids gave final judgment of no. 4 face

(awesome) for formula F2. Based on that, F2 was chosen to formulate the medicated candies.

The parameters mentioned in test evaluation were collected as final judgment of the participant kids in the evaluation of the medicated candies. Results are expressed in the figure 6.

3.3.3 Efficiency of preservative

Throughout the time of test, no growth of any microorganism was detected under the test conditions, whereas, the growth was observed in positive control tubes as illustrated in figure 7.

3.3.4 Preliminary stability study

Results of the Preliminary stability study are presented in table 6 and figure 8. The data showed the high stability of the prepared candies (Medicated F2) along the period of the test.

Table 5 :Total drug release from the tested formulas in 30 minutes in phosphate buffer 7.2, 37^{o}C and 50 rpm using apparatus II USP.

Formula	Medicated F2	F*
Percent drug release in 30 minutes.	88%	89%

Table 6: results of drug content of Medicated F2 at 40 ±1^{o}C , 75%RH.

Time (week)	0 (time of preparation)	1	2	3	4	8	12
Ibuprofen content (percent)	101 ± 1.3	99..5 ± 1.0	100.5±0.8	98.3±1.0	99.2± 0.9	101.2±0.9	99.2±1.0

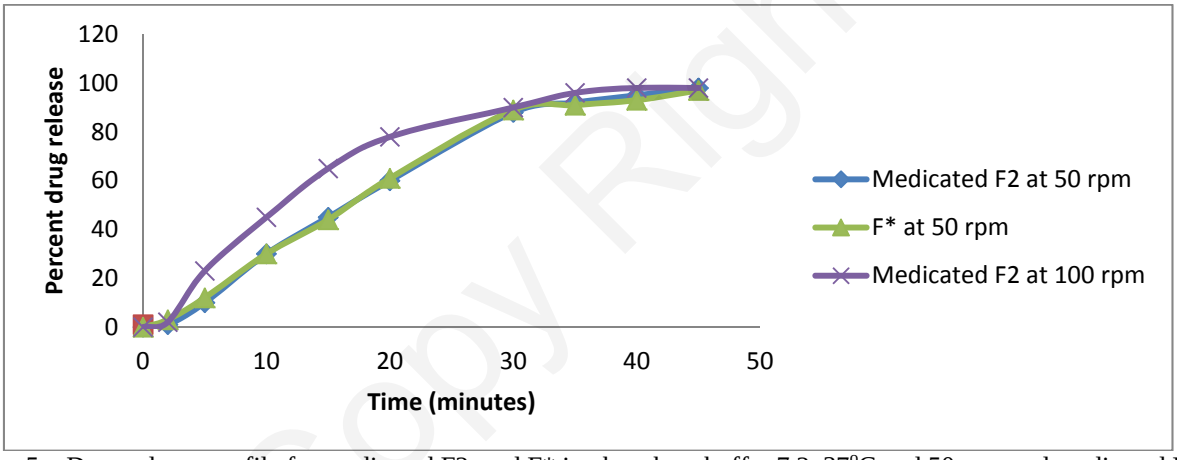

Figure 5: Drug release profile for medicated F2 and F* in phosphate buffer 7.2, 37^{o}C and 50 rpm and medicated F2 at 100 rpm.

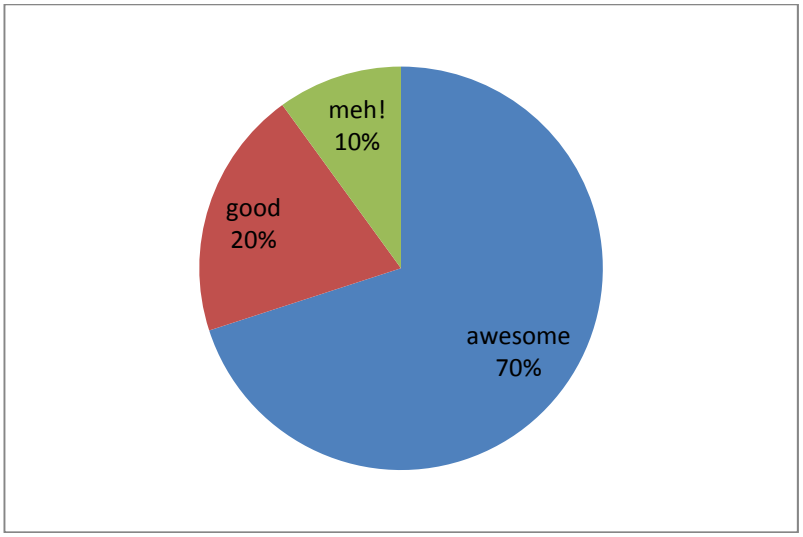

Figure 6: Results of taste evaluation of the medicated F2 candies.

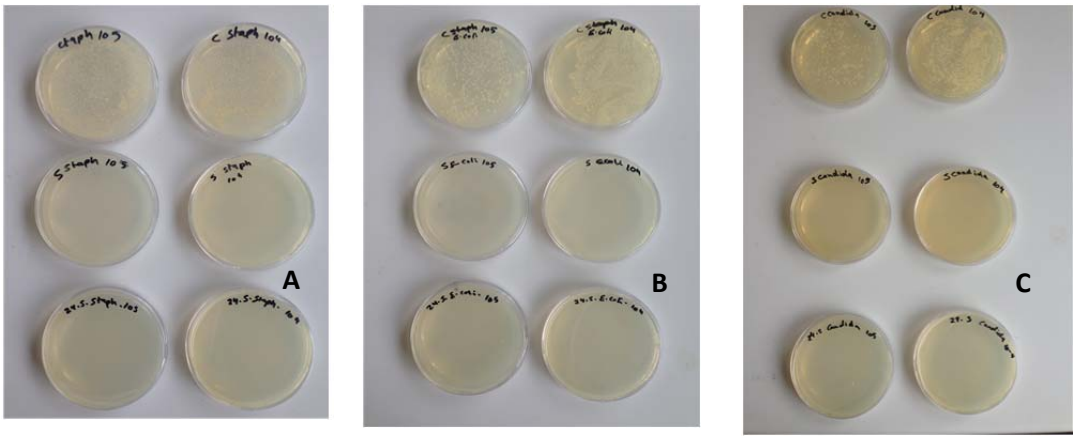

Figure 7: Results of preservative efficiency test.
A) *Staphylococcus aureus*. B) *Escherchia coli* and C) *Candida albicans.*

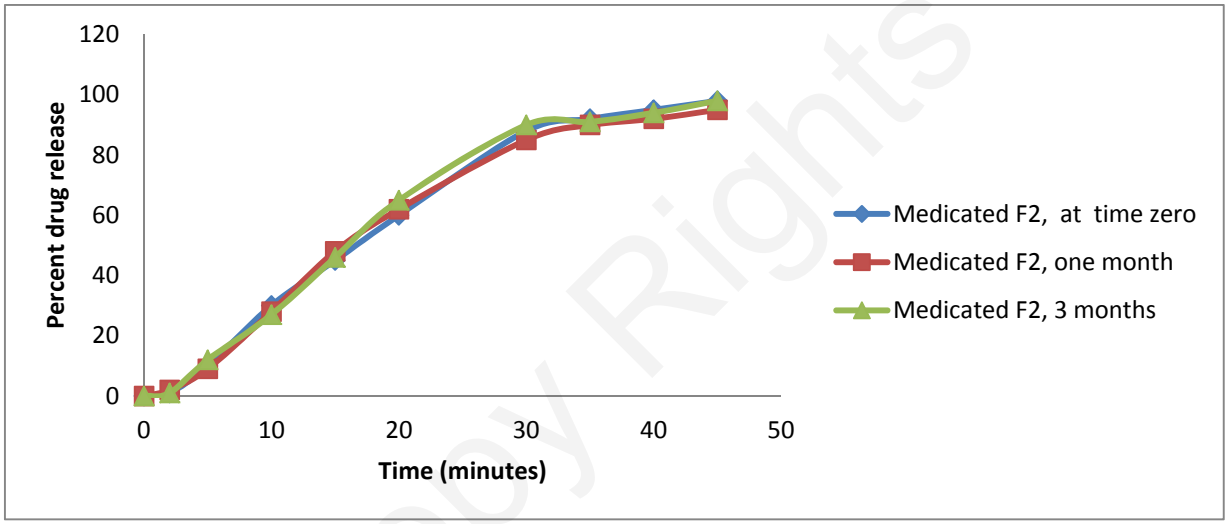

Figure8: Drug release profile of ibuprofen from medicated F2 in phosphate buffer pH 7.2, 37^{o}C and 50 rpm after 1 and 3 months of incubation in 40 ^{o}C and 75%RH.

CONCLUSION

Edible bovine gelatine candies can be used with Ibuprofen to produce accepted dosage form with good drug release for children which will help them take their medication easily and comfortablely.

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