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FORMULATION DEVELOPMENT AND EVALUATION OF OLMESARTAN MEDOXAMIL ORORETENTIVE JELLIES

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ABSTRACT
Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Olmesartan Medoxamil is an orally administered antihypertensive agent, used in the management of hypertension. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. Persons suffering from dysphagia may get choked when they consume liquid formulations, thus to alleviate such problem liquid formulation of high viscosity were prepared. Formulation of oral soft gel (batches of Olmesartan medoxamil) were prepared by using hydrophilic polymer almond gum and gelatin at three different concentration. The prepared batches were evaluated for appearance, viscosity, pH, drug content, syneresis and in vitro drug release. The optimized batch F5 were to be subjected to short term stability study for three months. The problem of dose measurement by patients was outweighed as oral medicated gels are to be packed in unit dose container.

KEYWORDS: Hypertension, medicated Jelly, Dysphagia, (OSML) Olmesartan medoxamil, almond gum, gelatin.

INTRODUCTION
Despite tremendous advancement in drug delivery, oral route remains the preferred route for the administration of therapeutic agent, because they have low cost of therapy and ease of administration leads to patient compliance. Development of novel drug delivery techniques that minimize toxicity and improve efficacy offers prospective benefits to patients and opens new avenues for pharmaceutical companies. Over a decade, the demand for development of oral medicated jellies (OMJs) has enormously increased as it has significant impact on the patient compliance. Oral medicated jellies are appreciated by a significant segment of populations particularly who have difficulty in swallowing. It has been reported that Dysphasia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients, psychiatric patients and patients with nausea, vomiting, and motion sickness complications. Common among all age groups, dysphasia is observed in about 35% of the general population, as well as up to 60% of the elderly institutionalized population and 18-22% of all patients in long-term care facilities. OMJs with good taste and flavor increase the acceptability of bitter drugs by various groups of population.

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Oral medicated jellies (OMJs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms.[1,2]

Olmesartan medoxomil is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. It is used for the treatment of patients with high blood pressure according to the drug label .Olmesartan is in a class of medications called angiotensin II receptor antagonists. It works by blocking the action of certain natural substances that tighten the blood vessels, allowing the blood to flow more smoothly and the heart to pump more efficiently. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis. Olmesartan has more than a 12,500-fold greater affinity for the AT1 receptor than for the AT2 receptor. [3,4,5]

Natural polymers are gaining importance as carriers of drugs in recent times. The advantages of these polymers over commercially available polymers are that they are biodegradable, biocompatible, nontoxic, low cost and environment friendly and locally available, better patient tolerated and edible. Almond gum as shown in Fig.1 and gelatin are recognized as viscosity enhancing agents and approved by US Food and Drug Administration (FDA) and are official in United States Pharmacopoeia (USP).They are popularly used as food additives and confectionaries and are generally regarded as safe.[6]

Fig. 1: Photograph of almond gum.

The present investigation is designed to improve patient compliance and ease of administration. Advantages of the olmesartan medoxamil oral jellies as a dosage form include increase in bioavailability, helps to bypass extensive hepatic first pass metabolism, reduction of dosage wastage, and etc. The present work is aimed at preparing a formulation of olmesartan medoxamil oral jellies, for treatment of hypertension.[4]

Criteria To Be Met By Drug Proposed To Be Formulated In Olmesartan Medoxamil Oral Jellies[5]

Some physicochemical parameters for selecting of drug to be formulated in Olmesartan Medoxamil oral Jellies as follows.

- The Drug should have Pleasant taste.
- It should be partially Unionized at the pH of oral cavity
- Drug should not affect the natural microbial flora of the mouth.
- Good solubility in water as well as in saliva and also good stability
- The drug should have high solubility and high permeability (BCS Class-I)
- The drug have extensive first pass metabolism.
- It should have quick onset of action.

1. MATERIALS AND METHODS

1.1. Materials

Olmesartan medoxamil was received as a gift sample from M/S. Glenmark Pharmaceuticals Ltd, Nashik. Gelling agents like gelatin and almond gum were brought from M/s. Modern Science, Nashik. All other chemicals and solvents used were of analytical grade.

1.2. Methods

1.2.1.|Preformulation studies[7]

Preformulation studies were performed for sample of drug identification and compatibility studies.

1.2.2. Organoleptic properties

The Organoleptic character of drug like odour, colour, taste and appearance play an important role in the identification of the sample and hence they should be recorded in a descriptive terminology.

1.2.3. Solubility studies: Solubility studies are an important consideration in formulation. The solubility of drug and polymer was tested with water and buffer solution.

1.2.4. Compatibility study of drug and polymer using FTIR

FT-IR Spectra were recorded with a Perkin Elmer FT-IR spectrophotometer in a range 400-400cm-1. Weighed quantity of drug (100mg) was mixed with potassium bromide (30mg). It was triturated in mortar and pestle and compressed under 5 ton pressure in a hydraulic pressure to form a transparent pellet. IR spectra for the pellet were determined to evaluate surface property of drug, polymer and their interaction hygroscopic in nature so it must be replaced in desiccators after using it.

1.2.5. Preparation of artificial saliva

Artificial saliva is prepared for the dissolution study of medicated jellies.[8,9] The compositions of artificial saliva are given in Table.1. The volumetric flask of 1 liter was used and adequate volume of water was added in it. Then all ingredients were weighed and added in it one after another and agitated constantly until fully dissolved. The adequate amount of distilled water was added to make volume up to 1 liter and was filtered using Whatmann filter paper.

Table 1: Composition of artificial saliva

Ingredients	Quantity
Sodium bicarbonate	5.208g
Dipotassium hydrogen phosphate trihydrate	1.369 g
Sodium chloride	0.877 g
Potassium chloride	0.477 g
Calcium chloride dehydrate	0.441 g
Distilled water	Quantity sufficient up to 1000 ml

1.2.6. Determination of λ_{max} for olmesartan medoxomil[10]

Olmesartan medoxomil was done by UV spectroscopy using artificial saliva and calibration curve of Olmesartan medoxomil was plotted by taking 2-18 µg/ml which was measured at 257nm.

1.2.6.1. Standard Calibration Curve of olmesartan medoxomil: Olmesartan medoxomil was quantitatively analyzed by various techniques. In the present study,

Olmesartan medoxomil was estimated by UV spectrophotometric method.

1.2.6.2. Preparation of standard calibration curve of olmesartan medoxomil in artificial saliva

Stock solution was prepared by dissolving 10.0 mg of olmesartan medoxomil in 10.0 ml of ethanol, made up to the volume to 100 ml with artificial salaiva which was further diluted to give the solutions of concentration 2, 4, 6, 8, 12, 14, 16 and g/ml respectively. Absorbance of these solutions were measured on UVspectrophotometer at 257 nm and plotted against the concentration to give the standard curve as shown in Figure.2.

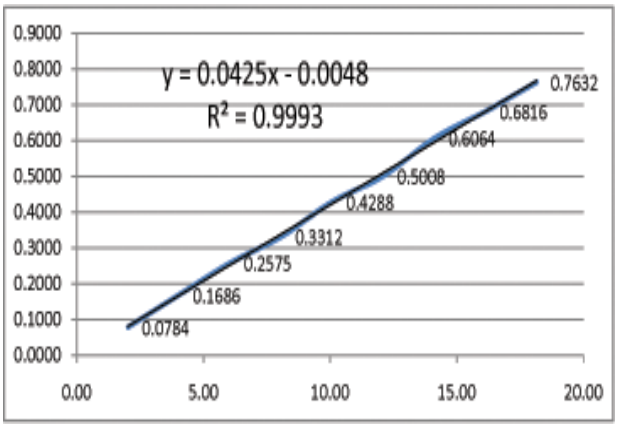

Fig. 2: Standard curve of olmesartan medoxomil.

1.2.7. Preparation method of jelly[11]

Jellies were prepared by heating and congealing method as shown in Table.2. Prepared using freshly boiled and cooled distilled water used. Sucrose syrup prepared in water on heating and stirring at 80^0c for about 90 minutes. Weighed polymer powder of almond gum and gelatin was dispersed in 10 ml of water maintained at 90^0c throughout the preparation. The dispersion was stirred using a magnetic stirrer for 20 mins to facilitate hydration of gelling agent. Drug taken in to another beaker and solubilized using alcohol. Simple syrup was added to it under continuous stirring. The citric acid and preservatives were added under continuous stirring at 60^0c. The final weight was adjusted with purified water, mixed, transfer to suitable moulds, sealed and allowed to cool that room temperature ($25^0\pm5^0$c) to form a jelly like texture as shown in Fig.3 . Finally, when jelly set it is wrapped in gelatin paper and stored in dry place.

Table 2: Formulation of olmesartan medoxamil oral medicated jellies.

Ingredients %	F1	F2	F3	F4	F5	F6	F7
Olmesartan medoxamil	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Almond Gum	0.3	0.3	0.4	0.4	0.5	0.5	0.5
Gelatin	0.3	0.4	0.3	0.4	0.3	0.4	0.5
Citric acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sugar syrup	66.7	66.7	66.7	66.7	66.7	66.7	66.7
Propylene glycol	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Propyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Raspberry flavor	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Amaranth color	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Distilled water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Each jelly weighs 1.4gms

Fig. 3: Oral Medicated Jellies of Olmesartan Medoxamil.

1.2.8. Evaluation Parameters[12]

1.2.8.1 General appearance

Texture and clarity of the soft gel was evaluated in terms of stickiness and grittiness by mildly rubbing the gel between two fingers. Consistency and odour were also evaluated by physical observation.

1.2.8.2. Rheological measurement

Viscosity of the all the batches of soft gels were measured using Brookfield DV-II+ Pro viscometer. The Olmesartan medoxamil containing soft jelly was squeezed out from the polyethylene plastic bag by making a cut of uniform size on the bag and viscosity was measured using spindle number LV4 at the rotation of 50 rpm at room temperature. The viscosity measurements were made in triplicate using fresh sample **2.** each time.

1.2.8.3. P_H of the soft jelly

The pH of the final gel has a great influence not only on stability, but also on the taste. The pH of olmesartan medoxamil containing soft jelly was measured using Electronic Digital pH meter at room temperature.

1.2.8.4. Syneresis

Syneresis is one of the major problems associated with almond gum gels. Syneresis means contraction of gel upon standing and separation of water from the gel. Syneresis is more pronounced in the gels where lower concentration of gelling agent is used. Gels were kept under scrutiny for signs of syneresis. The gels showing signs of syneresis were rejected and not considered for further studies.

1.2.8.5. Drug content

Take 10 jellies from jelly moulds in a beaker and there average weight was determined. They were breaked into gel consistency. Then gel equivalent 5.0 mg of OSML was taken in 100 mL volumetric flask and dissolved in 70 ml of ethanol with vigorous shaking for 5-10 min. Finally the volume was made up to the mark with ethanol. Finally it was analyzed in UV-spectrometer after proper dilution and filtration.

1.2.8.6. In vitro drug release

In vitro drug release studies was carried out using USP dissolution apparatus II using paddle at a speed of 75 rpm using 900 ml of artificial saliva as dissolution media containing 0.1% sodium lauryl Sulphate at 37±2°C. F5 formulations containing 20 mg of OSML medicated jelly was used in the dissolution test. 5 ml of sample was withdrawn at the interval of every 5 min and the drug solution was replaced with the same volume of artificial salaiva maintained at 37±2°C for 30 minutes. 1 ml of the filtered sample was diluted up to 50 ml with artificial saliva and absorbance was measured at 257 nm using UV-spectrometer.

1.2.8.7. Stability studies of soft gel

A physically stable oral gel retains its viscosity, color, clarity, taste, and odor throughout its shelf-life. Gels were checked for syneresis during storage. A freshly made sample should serve as a reference standard for subjective evaluations. The samples were kept at different temperatures for 3 months. The samples of soft gel were observed for pH, viscosity and appearance at the interval of one month. All the measurements were performed after allowing the samples to be equilibrated at 25°C for 2 hrs.

RESULTS AND DISCUSSION

2.1. Preformulation studies

The procured olmesartan medoxomil was white to almost white crystalline powder and odorless with slightly bitter taste. Melting was observed to be 180 °C ± 0.5°C. Loss on drying of was found to be 0.5% ±0.02%. It is slightly soluble in water and soluble in ethanol and methanol. Solubility studies were also performed in different buffer solutions to select the dissolution media which could maintain the sink conditions during in vitro release studies. The drug is slightly soluble in all buffers but has shown maximum solubility in P_H 6.8 (0.0425 mg/ml) and artificial saaiva which is similar to P_H 6.8 which was selected as a dissolution medium for in vitro dissolution study.

2.2. Drug-excipient compatibility studies

Physical examination of individual drug-excipient mixtures stored at 40°C and 75% RH was carried out for 45 days. The initial color of the drug-excipient mixtures observed as white to brownish for almond gum and white to off white for gelatin. All other excipients along with OSML showed white to off white color. No characteristic changes were observed in color or physical state for all the samples at 15, 30 and 45 days.

Infrared spectrum shows all prominent peaks of olmesartan medoxomil. IR spectrum of pure Olmesartan medoxomil shown in Figure.4 an absorption band was observed, peaks 2995.87 cm−1 (C-H, str, Sp2), 2923.56 cm−1 (C-H, str, Sp3), 1708 cm−1, 1832 cm−1 (C-O, str) and 3300–3100 cm−1 (N-H, str). These peaks can be considered as characteristic peaks of olmesartan medoxomil and were not affected and prominently observed in IR spectra of olmesartan medoxomil as shown in Figure 4, 5 and 6. No additional peaks corresponding to functional groups were obtained. There were no significant deviations found between the peaks of OSML and those of drug-excipient mixtures that indicated the stability of the drug in the presence of all excipients.

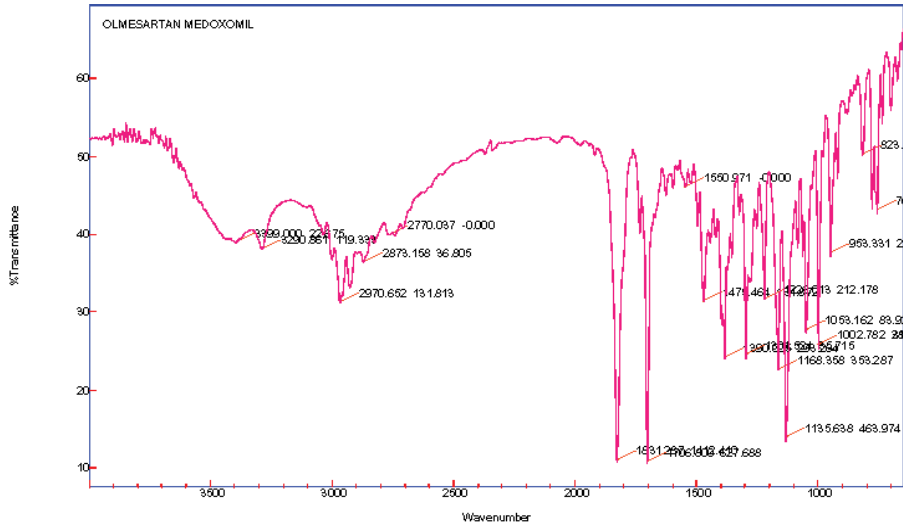

Fig. 4: FTIR spectrum of olmesartan medoxamil.

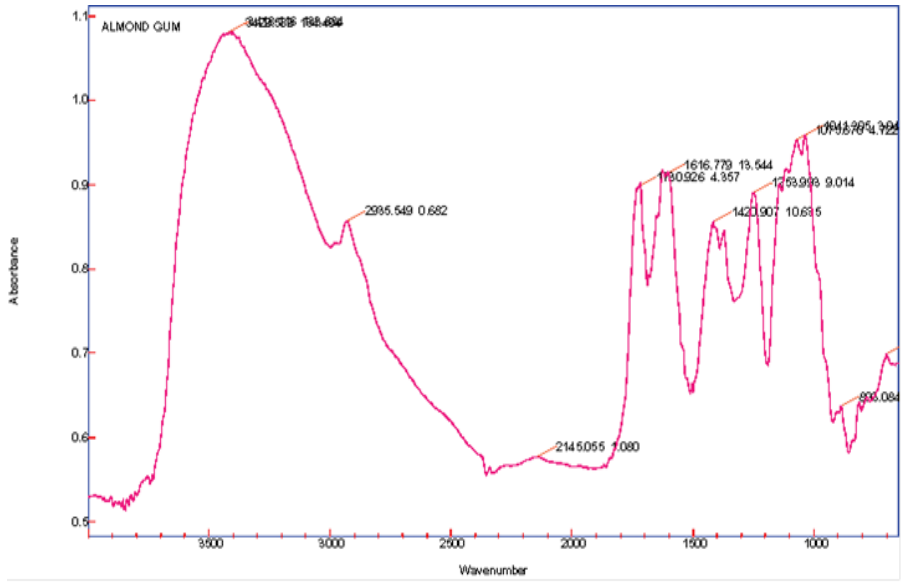

Fig. 5: FTIR spectrum of almond gum.

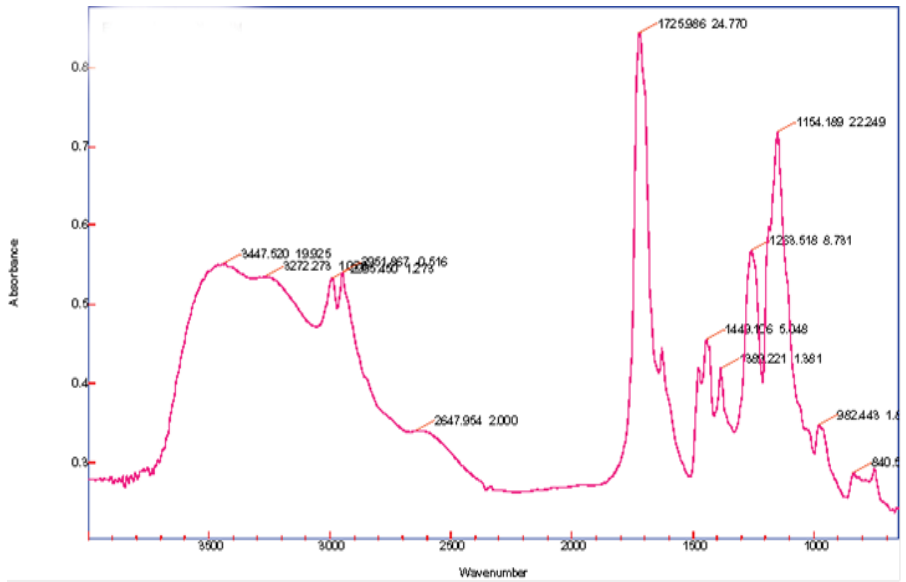

Fig. 6: FTIR spectrum of olmesartan medoxamil and almond gum.

2.3. General appearance

The physical appearance including clarity, precipitation, homogeneity, consistency as well as other features of the prepared OSML jellies were observed, that showed F5 formulations were clear, cherry red in color, having semisolid consistency, homogenous and have pleasant fruity aroma as shown in Fig.3. The stickiness and grittiness of the prepared OSML jelly were observed that showed the all the formulations shown to have stickiness and grittiness except F5,F6 and F7.` The results of various evaluation parameters of prepared jelly formulations are summarized in Table 3.

Table. 3: Physico - chemical properties of the oral jelly formulation.

Test parameters	Batch code						
	F1	F2	F3	F4	F5	F6	F7
Clarity	O	O	T	T	T	T	T
Consistency	NG	NG	G	G	G	G	G
Texture	SG	SG	SG	SG	NS&NG	NS&NG	NS&NG
Odour	P&F	P&F	P&F	P&F	P&F	P&F	P&F
PH (n=3)	6.54± 0.371	6.69± 0.453	6.06± 0.945	6.84± 0.675	6.75± 0.056	6.78± 0.543	6.63± 0.058
Viscosity (n=3)	1870	2570	4345	4583	5707	5798	6143
Syneresis at R.T	+++	+++	+++	++	-	-	-
Drug content (n=3)	96.75	97.45	98.51	97.56	98.04	98.73	98.85

O: opaque, T: Transparent, NG: Not good, SG: sticky and gritty NS &NG: Non sticky and non-gritty, P&F: Pleasant and fruity

2.4. P_H of jelly formulations

The pH of the formulation influences the taste and stability of oral jellies. The pH of the prepared formulations was found in the range of 6.06± 0.945 - 6.84±0.675 which was slightly acidic. Sucrose may precipitate in the presence of citric acid on standing [.13] Therefore, a minimum quantity of citric acid was added just to maintain the pH.

2.5. **Viscosity:** The viscosities of OSML jellies were found between 1870 and 6143 cps and varied depending on the type and concentration of polymer. Jellies prepared from almond gum as shown in Fig.7 alone showed low viscosity, but those prepared in combination with gelatin, the viscosity was increased and were found suitable as jelly formulations. The jellies of gelatin and almond gum employed alone showed higher viscosities. The concentration of the polymer directly influenced the viscosity.

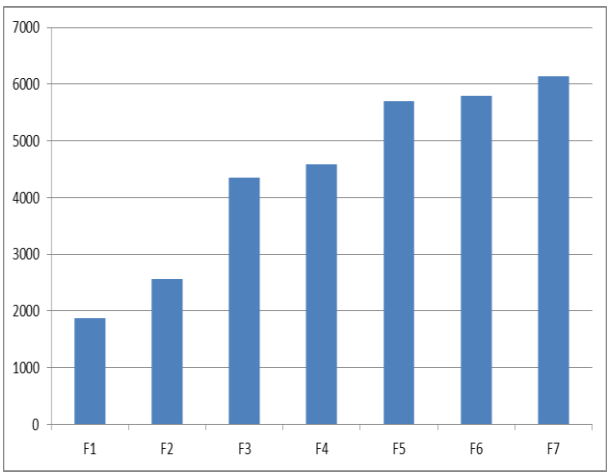

Fig. 7: Viscosity of different soft jelly batches F1 to F7.

2.6. Syneresis

Gels experience syneresis or de-swelling due to the release of liquid, resulting in shrinkage of gels and reduce quality [14] Syneresis was more pronounced in the gels, where lower but in acceptable limits. Raspberry flavor was chosen to help in masking the bitter taste of OSML, where lower concentration of gelling agent was employed. It was observed after 24 h of jelly preparation. All the formulations showed syneresis at room temperature (25°C ± 5°C) except F5,F6 and F7 as shown in Table 3. A reduction in the free energy of the system affects the water hold-up in the gels [.15] Syneresis was not noticed at room temperature probably due to binding of free water by co-solute[.16,17] In the preformulation studies, jellies containing almond gum and gelatin combination in higher concentration did not show syneresis. Hence, in order to reduce syneresis of almond gum jellies, gelatin was used as co-solute.

2.7. In vitro drug release study[18]

All samples of medicated jellies from F1 –F7 were analyzed by the UV-spectrophotometer at 257 nm to determine the drug concentration and amount of drug released. It was observed that F5 showed 97.30% drug released within 30 min as shown in Table. 4 and cumulative % drug release graph was drawn as shown in Fig.8. F5 batch was considered best formulation and further *in vivo* studies can be carried out. The rate of dissolution of best formulation F5 was higher and in conformity with the biopharmaceutics classification system concept for immediate release formulations (>85% in 20 min).

Table 4: Invitro % drug release of oral jellies

S.No	Formulation code	% Drug release after 30mts
1.	F1	89.74
2.	F2	90.35
3.	F3	91.74
4.	F4	94.56
5.	F5	97.30
6.	F6	95.70
7.	F7	95.28

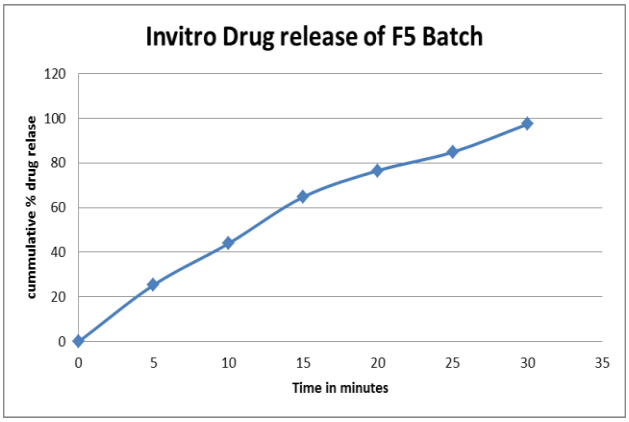

Fig. 8: Release of Olmesartan Medoxamil containing jelly batch F5 in artificial saliva

2.8. Stability studies [19]

A physically stable medicated oral jelly should retain its viscosity, color, clarity, taste, and odor throughout its shelf-life. The formulation F5 found to be stable in short term accelerated testing done for three months. There has been no significant change in physical appearance, pH, viscosity etc. as shown in Table.5.

Table 5: Stability studies of best formulation F5.

Parameter	Initial	After 1st month	After 2nd month	After 3rd month
Appearance	Transparent, opaque, milky white Semisolid jelly	No change	No change	No change
PH	7.3	7.5	7.6	7.6
Viscosity (dyne sec/cm2)	5710	5789	5958	5985
Temp 0 c	25	25	25	25
Drug content in (%)	98	95	93	93

3. CONCLUSION

To be concluded that prepared medicated jelly is more organoleptically accepted particularly by patients with disability in ingestion of food and drink, in other words, those having difficulty in mastication and swallowing. The present study concludes that oral medicated jellies containing olmesartan can be very promising for effective doses to systemic circulation. These may also provide an added advantage of circumventing the hepatic first pass metabolism. Prepared medicated jelly is cost wise cheap and acceptable and have gained relevance in pharmaceutical industry as a novel, patient friendly, convenient products.

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