FORMULATION AND EVALUATION OF MONTELUKAST SODIUM ORAL JELLY FOR PEDIATRICS

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ABSTRACT:

In the current research, Montelukast oral jelly was formulated. The objective behind the research was to develop Montelukast oral jelly using taste masking abilities especially for paediatric patients for the treatment of allergic conditions like hay fever or seasonal allergic rhinitis and asthma. The unique feature of oral jelly is that it is easily chewed and dissolves in saliva and hence doesn't require water. Moreover, Jellies are formed by aggregation of polymers with minimum two components; the gelling agent and the fluid component. Different batches were prepared using different concentrations of gellan gum (1%, 2%, 3% and 4%) and gelatine (1%, 1.5%, 2% and 2.5%) and prepared by the heating method. The prepared jelly was evaluated for the various parameters like appearance, pH, viscosity, texture, sugar crystallization, stiffness and invitro release study. The pH was found in the range of 6.9 ± 0.503 to 7 ± 0.404, viscosity increases with the increase in concentration of gelling agent, the prepared batches were non-sticky. invitro drug release study was performed by using simulated salivary fluid and percentage of drug release of formulation was found to be 58.52 to 92.08%. These parameters show satisfactory results therefore, the research opened new doors for bitter drugs.

KEY WORD: oral route, oral jellies, montelukast sodium, paediatrics

INTRODUCTION:

There are many routes from which drug can be administered and produce pharmacological response mainly common method is oral route. Oral route is the preferred route for better patient compliance and easy administration. The drug is swallowed and reach systemic circulation, the dose regimen is made according to the patient life style.

By oral route drug administration, the drug passes through the GIT, the drug is released from the dosage form in a solution at or near the optimal site for drug absorption to occur.GI fluid volume and motion can vary remarkably which has importance on drug dissolution and absorption. Additionally, transit time may also vary in various parts of the GIT depending upon the individual size and prevailing local conditions. (Gurleen kaur,2018)

The pharmaceutical dosage form passes through the gastrointestinal tract where the drug is released and available at the absorption site. The release rate from dosage form is into the solution is the main key for the kinetics of drug absorption. The potential to maintain these drugs in a soluble form as the drug proceed through the GI tract throughout the day has been a considerable challenge for oral formulators. (Guy Furness,2011)

Medicated Jellies can be defined as the gelatinous preparation having drug particles which are fused in it. Now-a-days, children are very much familiar to jelly candies as they are soft to chew and attractive too. and it may use as a well-liked design for drug administration as it is substitute to solid and liquid dosage form. Therefore, there is scope for more patient well coming delivery system especially by oral route. Paediatrics patient are more compliance with easy administration and more palatable and attractive dosage forms has knowing importance in the design of novel drug delivery system. (Gurleen kaur,2018)

As the jelly remain solid during storage for stability and it transformed into highly viscous liquid after its administration. Jellies are formed by intensification of polymers like gelatine, guar gum, gellan gum, pectin are widely used. By choosing the right gelling agent at suitable concentration, the drug released slowly from the jelly vehicle. The main aim is to develop the hydrophilic jelly dosage form for oral administration. (Panda BP,2012)

Types of Oral Jelly

There are three types of jellies: Medicated jelly: These are chiefly used on mucous membrane and skin for their spermicidal, local anaesthetics, and antiseptic properties. These jellies contain sufficient water. After evaporation of water, jellies provide a local cooling effect and residual film gives protection. For example, ephedrine sulphate jelly is used as a vasoconstrictor to arrest the bleeding of nose. Lubricating jelly: These jellies are used for lubrication of diagnostic equipment such as surgical gloves, cystoscopes, catheters Miscellaneous jelly: These are meant for various applications like patch testing, electrocardiography etc. (Mehta RM, 2003)

Material and methods

Montelukast sodium was received as a gift sample from windlass pvt. ltd Dehradun. All other chemicals and solvents used are of analytical grade and used as procured.

Preparation of montelukast sodium oral jelly:

1. The jellies were prepared by using different polymers of different quantities
2. The sugar syrup will be prepared.
3. To the sugar syrup the gelling agent is added with continuous stirring and heated.
4. As the gelling agent dissolves completely, stabilizers and solubilizes are added to it and boiled for few minutes, thoroughly mixed.
5. When the mixture was completely dissolved, preservatives are added to it with continuous stirring.
6. Then, drug was added to it with continuous stirring, colour and flavour was added, jellies could have settled down and thoroughly mixed.
7. The final weight was adjusted with purified water.
8. Then, transferred into moulds and the mixture could cool to room temperature to form jelly. **(table no.1)** (Raja Manali, 2016)

Evaluation of oral jelly

a. Organoleptic properties of jelly:

- **Appearance**: - It was examined visually the physical appearance in terms of consistency of medicated jelly.
- **Texture:** - It was examined physically the feel of touch on jelly surface.
- **Sugar crystallisation:** - It was examined by observing sugar crystals in medicated jelly
- **Stickiness and grittiness:** - It was evaluated visually by rubbing the jelly in two fingers. (Mangesh D Godbole, 2017)

b. pH: - pH was measured by using digital pH meter by dispersing 0.5 g of jelly in 50 mL of distilled water to make a 1% solution, and the pH was noted.

c. Viscosity: - Viscosity was measured by Brookfield viscometer using spindle no. 64 at 3 RPM at room temperature. (Bhoomika Shah,2012)

d. Spreadability: - Spreadability of jelly was determined by taking two slides on which 1000gm weight was kept and placing jelly in between the two slides and pressed for 5 minutes to a uniform thickness and the spreading area of jelly was calculated by using equation **($A = \pi r^2$)** it is represented as area of circle. This procedure was performed in triplicate and data was expressed as mean ± standard deviation. (uprit Shubham, 2013)

e. Weight variation: - The jellies was taken out from moulds and they are weighed individually. The average weight of 10 jellies was taken and the observed data was expressed as mean ± standard deviation.

f. Syneresis: - It was observed in jelly the shrinkage upon storage and break-up of water from the jelly. all jellies are noticed under room temperature for syneresis. The jellies which shows the signs of syneresis were discarded

g. Taste analysis: - Taste was analysed by masking the taste having 5ml of phosphate buffer 6.8 in 50ml beaker with one jelly and then allowed for 60 sec and 120 seconds to stand. After that, the solution was filtered and analysed by U.V spectrometer. The taste determination was done according to the bitterness scale range: **table no.2**

h. Drug content uniformity: - Montelukast sodium jellies were taken to test the drug content uniformity to check that each dosage form holds equal amount of active pharmaceutical ingredient (API). All formulations jellies were subjected for content uniformity test by using phosphate buffer 6.8 and analysed by U.V spectrometer under maximum wavelength 360 nm.

i. Invitro drug release: - Invitro drug dissolution of jelly was achieved with USP paddle apparatus type 2 using 900ml phosphate buffer 6.8 as dissolution medium at 50rpm. The temperature 37˚ C ± 0.5 ˚C was maintained. 5ml of sample was withdrawn from the dissolution apparatus at defined time intervals 5, 10, 15 20, 25, 30, 35, 40 and 5ml solution was exchanged with fresh dissolution media. The release manner was determined by using U.V spectrometer and release study calculated by kinetic models. (Melissa R Cardoz,2017)

Result and discussion

1. Organoleptic properties: the observed organoleptic properties showed in table no.3

Discussion: From all formulation we concluded that each batch having smooth texture. Although appearance is translucent in all formulations but the FJ1 contains littles bubbles in it, FJ4 is slightly thick and FJ2 & FJ3 formulation having uniform consistency. While formulation F2 to F4 exhibit no such stickiness and grittiness. The formulation FJ1 & FJ2 show no sugar crystallisation means sugar is properly dissolved in mixture i.e no crunches are present. It was concluded that FJ2 & FJ3 formulation showed acceptable jelly formulation.

2. pH: the pH was measured showed in table no.4

Discussion: The pH determines the taste and stability of jellies formulation and found in the range of 6.9 ± 0.503 to 7 ± 0.404 which is near to neutral. So, minimum amount of citric acid is added to maintain the pH.

3. Viscosity: flow properties are being observed table no.5

Discussion: the viscosity was found in the range of 45600 to 29200 cps. As the viscosity is decreased the drug flow increases.

4. Spreadability: the Spreadability is being observed table no.6

Discussion: the spreadability of formulation was found to decrease with the increasing the concentration of gelling agent.

5. Weight variation: the weight variation of jellies is measured table no.7

Discussion: the weight variation varies from 0.811± 0.0385 gm to 0.91±0.0306gm.

6. Synersis: de-swelling is observed table no.8

Discussion: there was no syneresis observed in the optimized formulation at the specified temperature.

7. Taste analysis: taste of jellies is observed table no.9

Discussion: the taste determination was found in the range of 0.87% to 1.82% which lies in scale range of no bitterness and threshold bitter. Hence, it can be co-related to taste feel.

8. Drug content uniformity: table no.10

Discussion: the drug content of formulation FJ2 was found to be 99.12%

9. Invitro drug release studies: table no.11

Discussion: The invitro drug release of formulation FJ1 to FJ4 were studied. All formulation shows different level of drug release ranging from 58.52 to 92.08%. it has been evaluated that as the low concentration of gelling agent shows the significant drug release FJ1 & FJ2 (89.81 % & 92.08 %). The formulation FJ1 and FJ2 containing lowest concentration of gelling agent.

Kinetic studies: table no.12

Discussion: Drug release kinetic model are used to illustrate the drug release mechanism. For this various model are used like zero order, higuchi, first order, korsmeyer peppas to obtain the value of R^2 value and n-value for the determination of best fit model. R^2 value was compared for all the formulation which shows the best fit model and by noticing n-value which is obtained from korsmeyer peppas model. Release mechanism was described by an equation:

$$\mathbf{Mt/M\infty = kt^n}$$

Followed by standard release mechanism table 13.

The observed data of kinetic model shows the best fit model for prepared oral medicated jelly was determined by regression coefficient(r^2) in all formulation. The highest r^2 value determine the best fit model, the observed data shows the zero- order release in all formulation i.e, the drug release is independent of concentration. Formulation FJ1, FJ2 & FJ4 shows the non-fickian diffusion and FJ3 shows the supercase II transport which depends upon the loss of polymeric chain and the release of drug takes place.

Table no.1: Formulation table

Ingredients	FJ1	FJ2	FJ3	FJ4
Montelukast sodium(mg)	5	5	5	5
Gelatine (%)	1	1.5	2	2.5
Gellan gum (%)	1	2	3	4
Glycerine(ml)	3	3	3	3
Citric acid (%)	1	1	1	1
Propylene glycol(ml)	3	3	3	3

Sugar (%)	60	60	60	60
D.w	q.s	q.s	q.s	q.s

Table no. 2: Taste analysis

Range	Bitterness level
0	No bitter
1	Threshold bitter
2	Slight bitter
3	Moderated bitter
4	Bitter
5	Strong bitter

Table no. 3: Organoleptic properties

Formulation code	Appearance	Texture	Sugar crystallisation	Stickiness and grittiness
FJ1	Translucent but water bubbles are found	Smooth	No	Slightly sticky & gritty
FJ2	Translucent with uniform consistency	Smooth	No	Non-sticky & less gritty
FJ3	Translucent with uniform consistency	Smooth	No	Non-sticky & less gritty
FJ4	Translucent but slightly thick	Smooth	No	Non-sticky & less gritty

FORMULATION J1 **FORMULATION J2**

Formulation code	pH ± S.D (n=3)
FJ1	7 ± 0.404
FJ2	6.8 ± 0.321
FJ3	6.7 ± 0.267
FJ4	6.9 ± 0.503

FORMULATION J3

FORMULATION J 4

Table no. 4: pH Detrmination

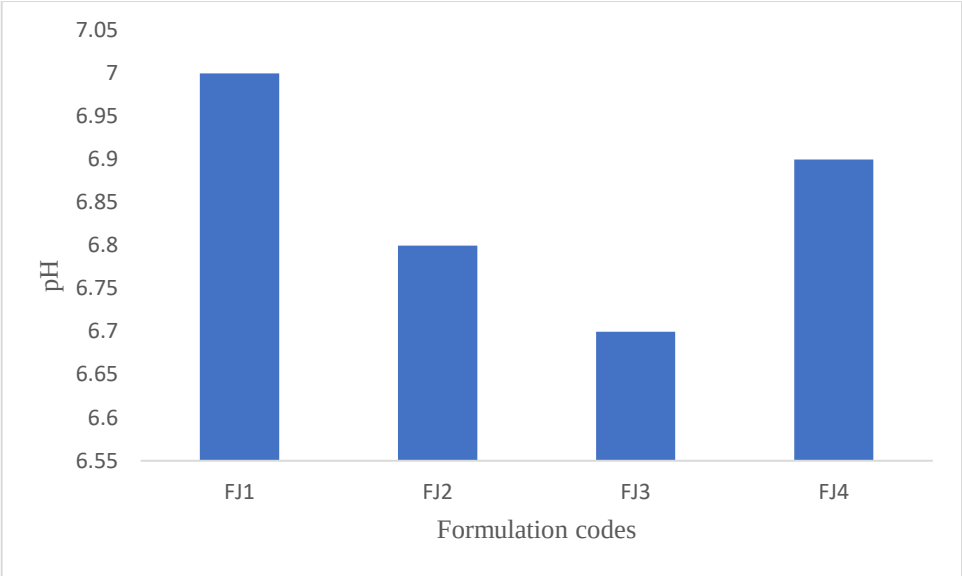

Figure no. 1 pH determination between formulation codes and pH

Table no. 5: Viscosity determination

Formulation code	**Viscosity (cps)**
FJ1	36200
FJ2	29200
FJ3	45000
FJ4	45600

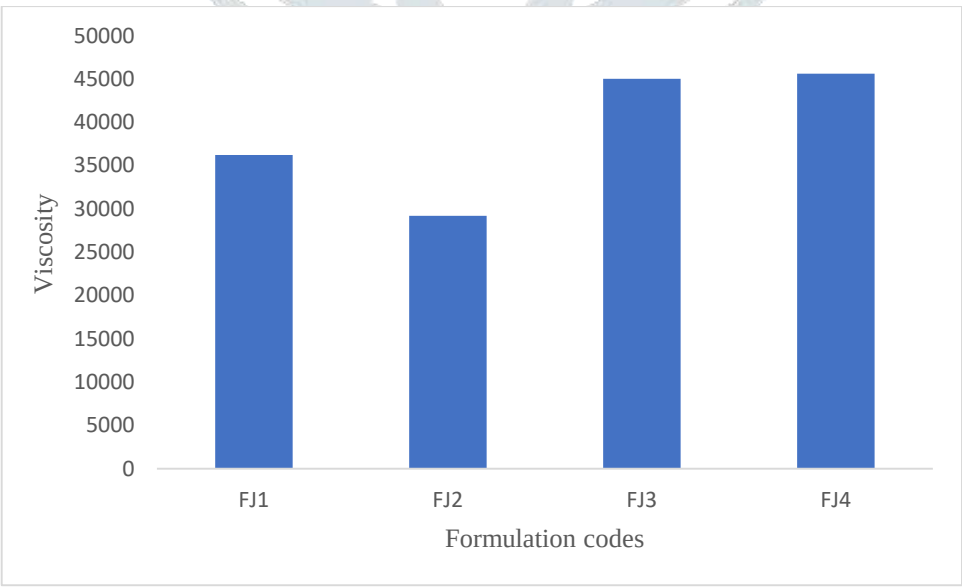

Figure no. 2 Viscosity determination between formulation codes and viscosity

Table no. 6: Spreadability

Formulation code	Spreadability ± S.D (n=3) (cm^2)
FJ1	21.22±0.15
FJ2	19.62±0.09
FJ3	13.84±0.12
FJ4	12.56±0.16

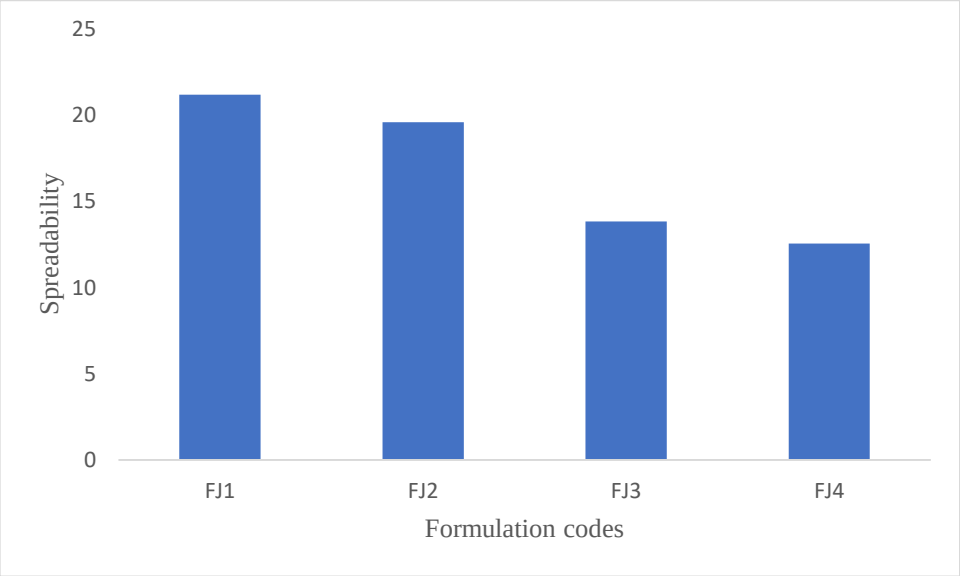

Figure no. 3 spreadability determination

Table no. 7: Weight Variation

Formulation code	Weight variation ± S.D (n=3)
FJ1	0.89± 0.0219
FJ2	0.811±0.0385
FJ3	0.91±0.0306
FJ4	0.877±0.023

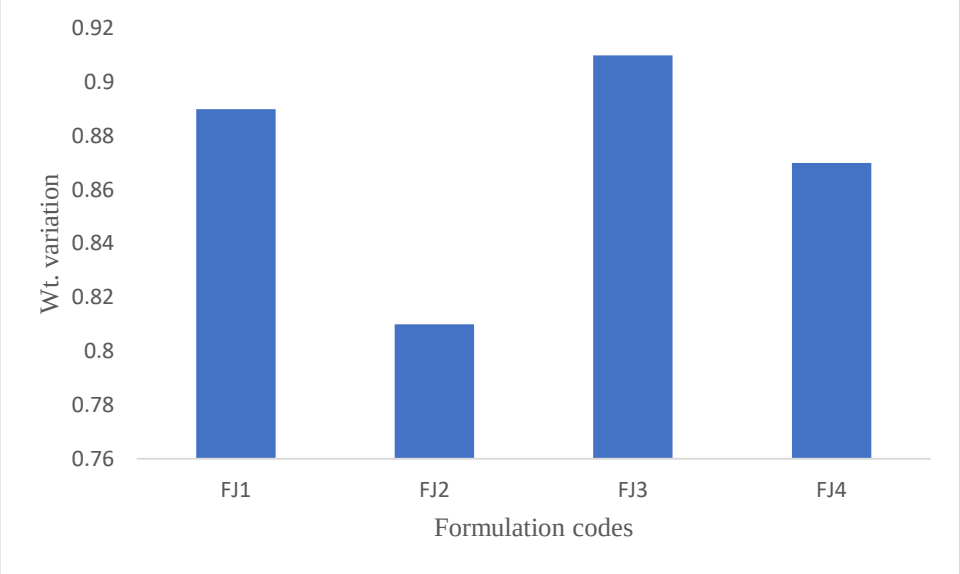

Figure no. 4 Weight Variation

Table no. 8: Synersis

Formulation code	**Synersis**
FJ1	No
FJ2	No
FJ3	No
FJ4	No

Table no. 9: Taste analysis

Formulation code	**Taste analysis**
FJ1	1.82%
FJ2	0.97%
FJ3	0.92%
FJ4	0.87%

Table no. 10: Drug content

Formulation code	**Drug content ± S.D (n=3)**
FJ1	98.66±0.428
FJ2	99.12±0.502

FJ3	96.68±0.297
FJ4	97.51±0.492

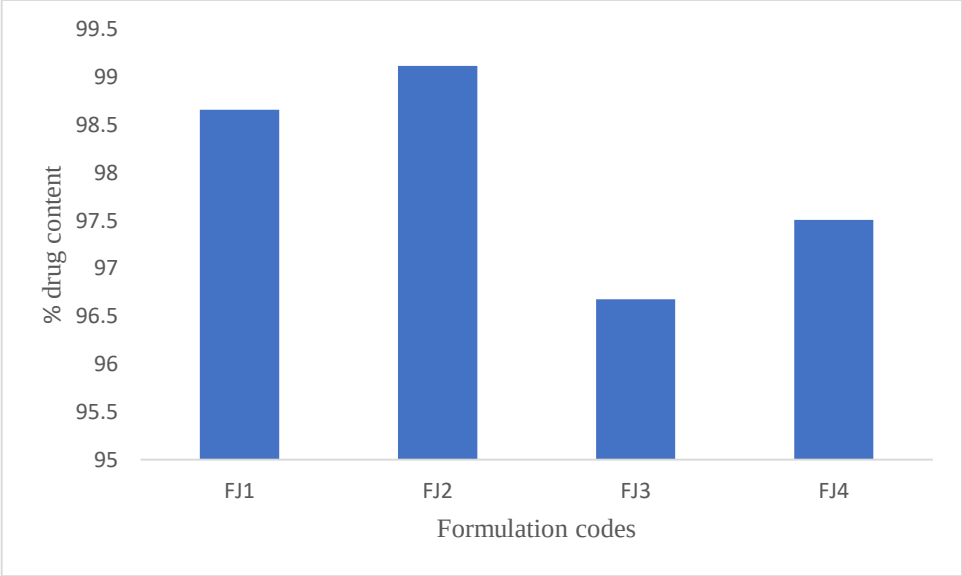

Figure no. 5 Drug content measurement

Table no. 11: Invitro drug release

S.no.	Time (min)	Cumulative percent drug release (%C.R)			
		FJ1	**FJ2**	**FJ3**	**FJ4**
1	0	0	0	0	0
2	5	23	20.28	14.28	11.5
3	10	28.43	28.04	19.8	18.14
4	15	33.65	39.81	23.95	26.94
5	20	43.57	52.26	31.28	31.94
6	25	59.33	64.50	40.71	34.32
7	30	74.85	77.69	45.71	39.54
8	35	80.41	85.81	59.99	44.44
9	40	89.81	92.08	69.39	58.52

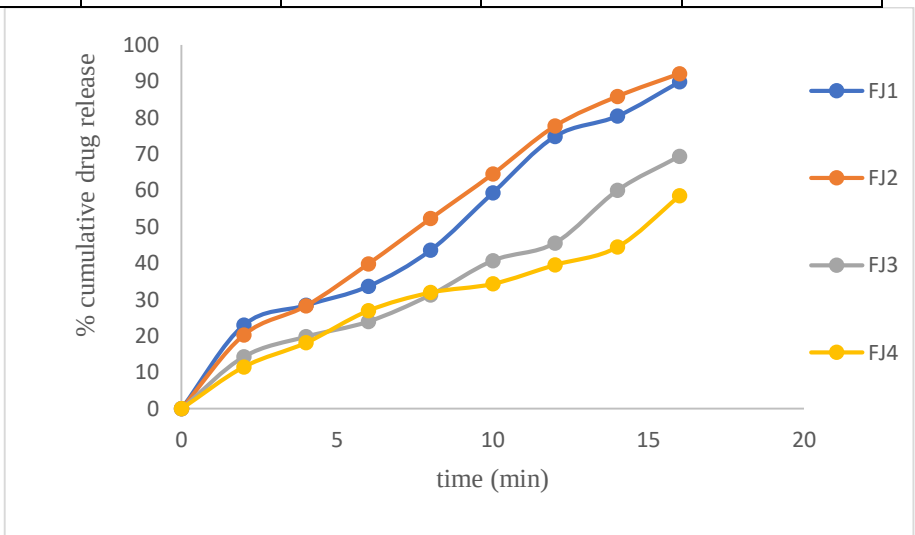

Figure no. 6 Invitro drug release between percent cumulative drug release and time

Table no. 12: Drug release kinetic with model fitting:

Formulation Code	R^2			n value	Best fit model	Mechanism of release
	Zero order	First order	Higuchi matrix			
FJ1	0.980	0.9204	0.923	0.6975	Zero order	Non- fickian diffusion
FJ2	0.9897	0.9453	0.9488	0.7764	Zero order	Non- fickian diffusion
FJ3	0.9814	0.9182	0.8975	1.6584	Zero order	SupercaseII transport
FJ4	0.9686	0.9209	0.9382	0.7314	Zero order	Non- fickian diffusion

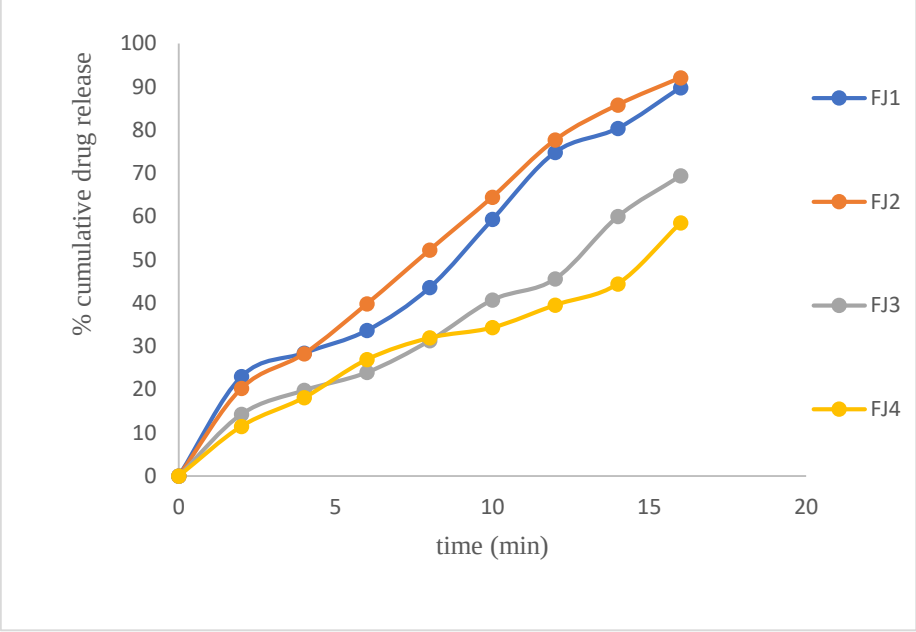

Figure7: kinetic release model of zero order release between Cumulative %drug release and time

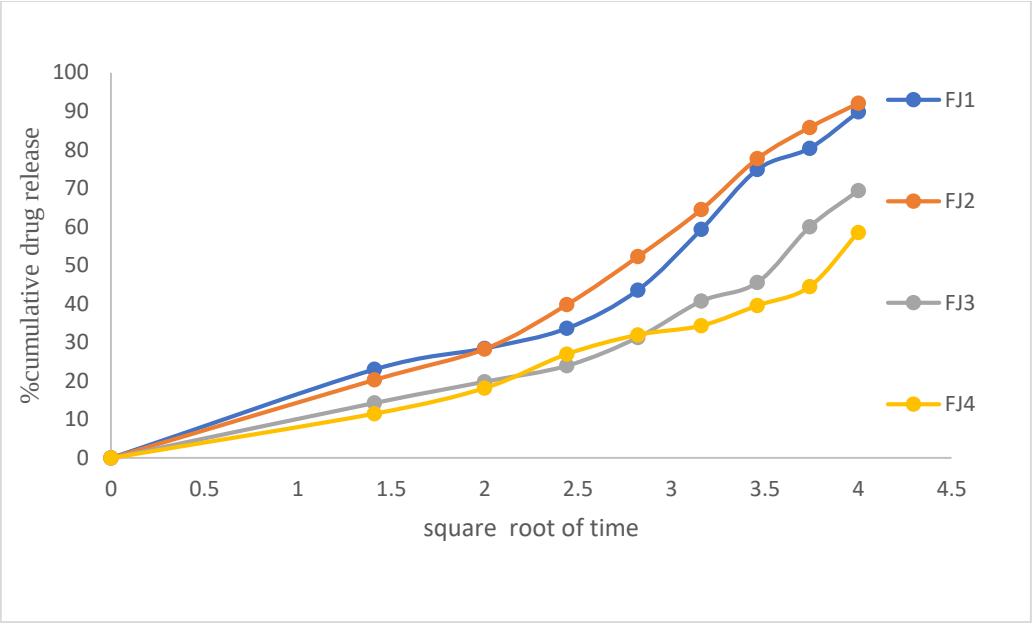

Figure 8: kinetic release model of higuchi release between Cumulative %drug release and square root of time

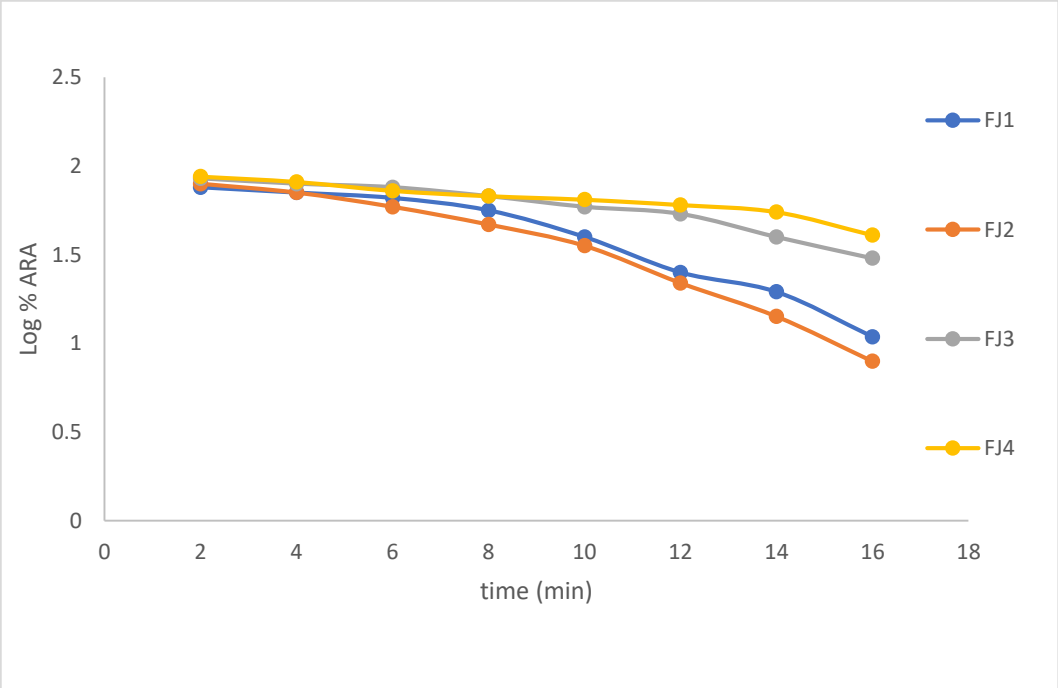

Figure 9: kinetic release model of first order release between log Cumulative %drug release and time

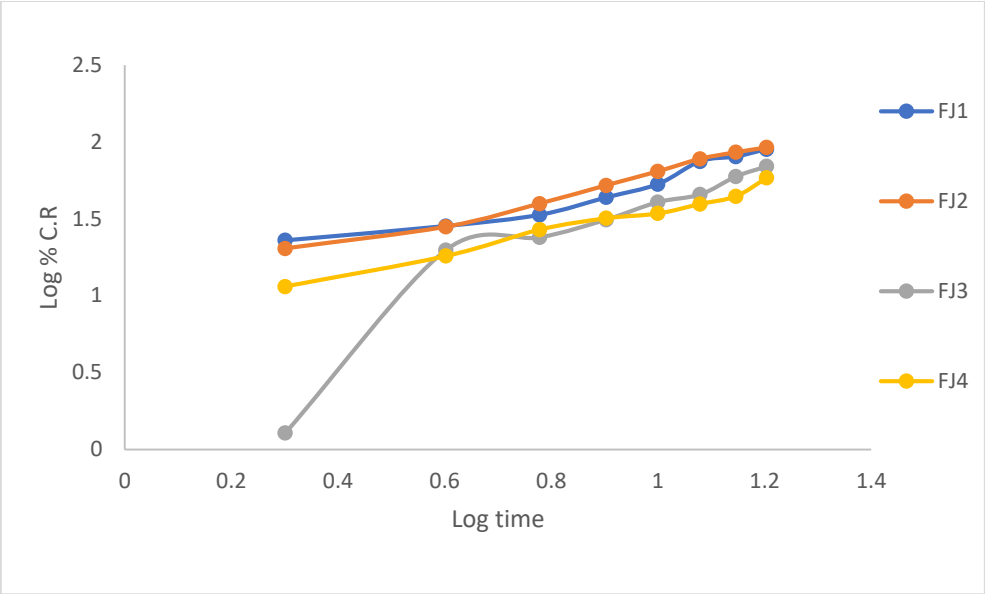

Table no.13: Followed by standard release mechanism table:

n value	**Release mechanism**
0.5	Fickian diffusion
0.5<n<1	Non – fickian diffusion
1	Supercase II transport

CONCLUSION: It was concluded that optimized formulation of Montelukast jelly shows better dosage form because it will give quick relief in allergic conditions like itching, sneezing, rhinitis etc. Moreover, Montelukast jelly can be taken by orally and chewed without ingestion of water. This will surely promote high patient acceptance and compliance. The formulation FJ2 &FJ3 having uniform consistency and bears no such stickiness and gritiness. Sugar crystals are also not present if was there it will cause hinder in chewing jelly. The pH determines the taste and stability of jellies formulation and found in the range of 6.9 ± 0.503 to 7 ± 0.404 which is near to neutral. So, minimum amount of citric acid is added to maintain the pH. Jellies are strong and elastic when shear stress is applied they tend to rupture and crumble and flow under the effect of higher shear stress and found in the range of 45600 to 29200 cps as the viscosity is decreased the drug flow increases. Spreadability is tested to check the jelly is not brittle and hard or any other grittiness is present. The Spreadability of formulation was found to decrease with the increasing the concentration of gelling agent and should spread to mouth cavity as the thickness get reduced. The weight variation varies from 0.811± 0.0385 gm to 0.91±0.0306gm. There was no syneresis observed in the optimized formulation at the specified temperature means de-swelling. The taste determination was found in the range of 0.87% to 1.82% which lies in scale range of no bitterness and threshold bitter. Hence, it can be co-related to taste feel better and can be easily taken by paediatrics. The drug content of formulation FJ2 was found to be 99.12%. the invitro drug release of formulation FJ1 to FJ4 were studied. All formulation shows different level of drug release ranging from 58.52 to 92.08%. it has been evaluated that as the low concentration of gelling agent shows the significant drug release FJ1 & FJ2 (89.81% & 92.08 %). The formulation FJ1 and FJ2 containing lowest concentration of gelling agent. Various kinetics models are prepared like zero order, higuchi, first order, korsmeyer peppas models. The highest r^2 value determine the best fit model and the n-value determines the mechanism of drug release. The observed data shows the zero- order release in all formulation i.e, the drug release is independent of concentration. Formulation FJ1, FJ2 & FJ4 shows the non-fickian diffusion and FJ3 shows the supercase II transport which depends upon the loss of polymeric chain and the release of drug takes place.

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