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DESIGN AND CHARACTERIZATION OF TRAMADOL HYDROCHLORIDE SOFT LOLLIPOPS

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ABSTRACT

The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation. The illness are associated with fever, head ache and body aches so to cure the above/relief from the above, there was need to administer the drugs to the individuals but in case of pediatric patients it was difficult to administer the dosage forms like tablets, capsules, etc. In the present investigation an attempt has been made to prepare and evaluate the sugar based medicated tramadol hydrochloride soft lollipops for pediatrics to overcome the administration. They were prepared by heating and congealing method on laboraty scale with malt syrup as base. All the formulations were subjected to various physico-chemical parameters such as hardness, friability, content uniformity, weight variation, thickness, drug content and in vitro dissolution studies. Drug-excipients compability stuidies were conducted by FT-IR spectroscopy and results revealed that no interactions were found between drug and excipients. The results of in vitro drug release studies showed that formulations F30, F33 and F36releases the drug 94.4, 97.7 and 93.8 percentage at the end of 30 mins. The soft lollipops can provide an attractive alternative formulation in the treatment of pain in pediatric patients.

KEYWORDS: Tramadol Hydrochloride lollipops, HPMC: Hydroxy Propyl Methyl Cellulose, Na CMC: Sodium Carboxyl Methyl Cellulose, MC(Methyl Cellulose).

INTRODUCTION

In oral drug delivery, there are many challenges that could be studied for years to come, and invention technologies are required to generate novel dosage forms raising drug delivery to higher level. Oral controlled release drug delivery is a drug delivery system that provides the unremitting oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid, dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydro dynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. To design the oral controlled release tablet to increase the residence time of the drug in to the stomach and release for extended period of time in order to Increase bioavailability of the drug, reduce the dosing frequency, Improve patient compliance. Interest in controlled and sustained release drug delivery has increased considerably during the past decade and, in selected areas, it's now possible to employ fairly sophisticated system which is capable of excellent drug release control.

LOLLIPOPS

Development of lozenges dates back to 20th century and is still in commercial production. Most of the lollipops preparations are available as Over the Counter medications. Lollipops provide a palatable means of dosage form administration and enjoy its position in pharmaceutical market owing to its several advantages but it suffers from certain disadvantages too. A small, medicated candy, originally in the shape of a lozenge intended to be dissolved slowly in the mouth to lubricate and soothe irritated tissues of the throat. Lollipops are the solid unit dosage form containing one or more medicaments usually in a flavored, sweetened base that dissolve slowly in the mouth or pharynx or that can be easily chewed and swallowed are gaining in popularity, especially among pediatric patients.

Lollipops are most often used for localized effects in the mouth. They can also be used for systemic effect if the drug is well absorbed through the buccal lining or is swallowed. Newer drugs include analgesics, anesthetics, and antiseptics, antimicrobials, anti tussives, anti-nausants, and decongestants.

SOFT LOLLIPOPS

Soft lollipops have become popular because of ease with which they can be extemporaneously prepared and their applicability to a wide variety of drugs. The bases usually consist of a mixture of various PEGs, acacia, or similar materials .an alternative and older form of soft lozenges is the pastille, which is a soft lozenge, is usually transparent and consists of a medication in a gelatin, Glycero gelatin, or an acacia: sucrose base. These lollipops may be colored and flavored, and they can be either slowly dissolved in the mouth or chewed, depending on the intended effect of the incorporated drug. Because of their soft texture, these lollipops can be hand rolled and then cut into pieces which contain the correct amount of active ingredient. But a more convenient dispensing method is to pour the warm mass into a plastic troche mold.

MATERIALS

Pure drug samples of Tramadol were obtained as gift samples from Dr.Reddy's Laboratories, Hyderabad. Sucrose, HPMC, Sodium carboxy methyl cellulose was obtained as gift sample from BASF suppliers. Methyl cellulose, Citric acid, GlyceroGelatinbase was purchased from Loba chemicals.

PREFORMULATION STUDIES

Construction of calibration curve for tramadol hydrochloride

Accurately weighed 100 mg of tramadol hydrochloride was transferred into100ml volumetric flask and dissolved in 6.8pH phosphate buffer and the solution was made upto 100 ml with 6.8 pH phosphate buffer. From this stock solution a series of dilutions of 2,4,6,8and10 µg/ml concentrations were made. And the absorbance was measured by using Shimadzu UV-spectrophotometer at 271 nm.

Table no. 1: Calibration data of Tramadol hydrochloride.

Concentration (µg / ml)	Absorbance ($\overline{X}$ ±S.D)
0	0
2	0.031± 0.002
4	0.068± 0.003

6	0.101± 0.004
8	0.132 ± 0.005
10	0.164± 0.005

LINEAR REGRESSION EQUATION

Linear regression analysis was performed to obtain equation for straight line Equation for calibration curve of tramadol hydrochloride is Y=0.016X+0.04.

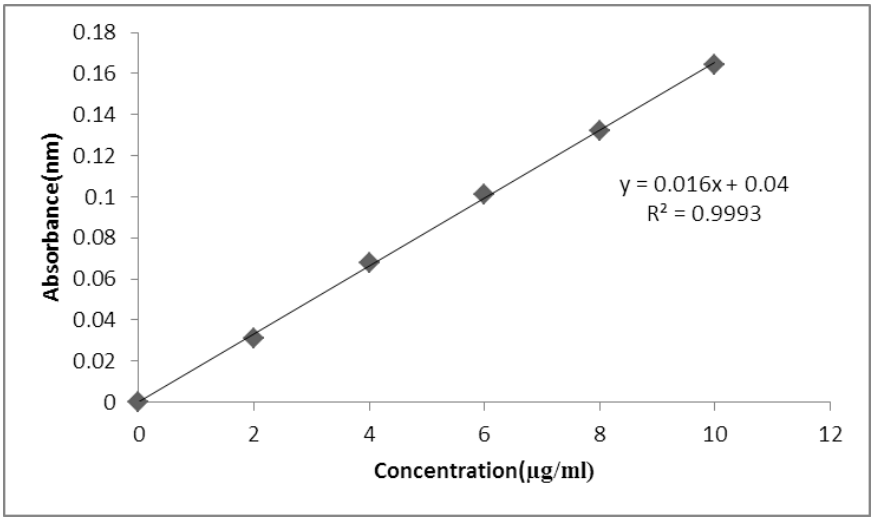

Fig no. 1: Calibration Curve of Tramadol Hydrochloride.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

The compatibility studies for Tramadol hydrochloride, polymers (HPMC,MC, NaCMC)and physical mixtures between tramadol hydrochloride and polymers used in the present investigation was studied out by FTIR spectrophotometer. The spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The spectra obtained for Tramadol hydrochloride, HPMC, NaCMC, Methyl cellulose and its physical mixtures of the drug and polymers.

PREPARATION OF SOFT LOLLIPOPS

Soft lozenges were prepared by using glycerol gelatin base, required amounts of drug, sucrose and polymers like HPMC, NaCMC and Methyl cellulose and drug were added. This preparation was done by heating and congealing technique. The material was poured on a mould and placed in freezer until it was solidified. The prepared lozenges were seal wrapped in polythene wrappings. An altogether three batches of formulations were prepared i.e., Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Carboxy Methyl Cellulose (Na CMC), Methyl Cellulose.

Table No. 2: Composition of Soft Lozenges Using Different Polymers.

S.no	Ingredients	Formulations								
		F28	F29	F30	F31	F32	F33	F34	F35	F36
1	Drug(mg)	23	23	23	23	23	23	23	23	23
2	Glycerogelatin base(gm)	2.6	2.4	2.2	2.6	2.4	2.2	2.6	2.4	2.2
3	Sucrose(gm)	1	1	1	1	1	1	1	1	1
4	HPMC(3000 cps)(mg)	100	300	500	_	_	_	_	_	_
5	Sodium Carboxy methyl cellulose(mg)	_	_	_	100	300	500	_	_	_
6	Methyl cellulose(mg)	_	_	_	_	_	_	100	300	500
7	Citric acid(mg)	50	50	50	50	50	50	50	50	50
8	Calcium carbonate(mg)	5	5	5	5	5	5	5	5	5

EVALUATION OF PHYSICAL PROPERITIES OF LOLLIPOPS

1. THICKNESS

The thickness and diameter of the formulated lollipops were measured by using Vernier calipers.

2. WEIGHT VARIATION

The formulated lollipops were tested for weight uniformity. 20 tablets were collectively and individually. From the collective weight, average weight was calculated. Each lollipops weight was then compared with average weight to ascertain whether it is with in permissible limits or not.

$$\% \text{ Weight Variation} = \frac{\text{Average weight-Individual weight}}{\text{Average weight}} \times 100$$

3. HARDNESS

The lollipops crushing strength, which is the force required to break the lozenge by compr**ess**ionin the diametric direction was measured in triplicate using Pfizer tablet hardness tester.

4. FRIABILITY

The Roche friability test apparatus was used to determine the friability of the lollipops. 5 pre weighed lollipops were placed in the apparatus, which was subjected to 100 revolutions. Then the lollipops were reweighed. The percentage friability calculated was using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight- Final weight}}{\text{Initial weight}} \times 100$$

5. DRUG CONTENT

Lollipops were weighed and powdered. The quantity of powder equivalent to 100 mg of tramadol hydrochloride was dissolved in 6.8 pH phosphate buffer diluted to 100ml with6.8 pH phosphate buffer then the solution was filtered and suitably diluted. The drug content was estimated spectrometrically at 271 nm.

IN VITRO DISSOLUTION STUDIES

Dissolution rate was studied using USP II paddle dissolution apparatus, in 900ml of Tramadol hydrochloride 37±0.5°at 100 rpm. Aliquot of dissolution medium withdrawn at regular time intervals and the same volume of pre-warmed (37±0.5°) fresh dissolution medium was replaced. The samples were filtered and drug content of Tramadol hydrochloride in each sample was analyzed after suitable Dilution by Shimadzu UV-spectrophotometer at 271 nm.

RESULTS

Table no. 3: IR-spectral values for physical mixture of drug and excipients.

Functional group	Observed wave number (cm-1)			
	Tramadol hydrochloride	Physical mixture of Tramadol hydrochloride with		
		HPMC	NaCMC	MC
O-H stretching	3305.25	3305.83	3305.61	3305.77
C-Ostretching of ethers	1045.70	1045.65	1045.28	1045.63
C-H stretching of alkyl group	2930.45	2930.29	2929.90	2930.25
C-H deformation of alkyl group	1480.42	1479.98	1480.36	1479.82
C=C of aromatic ring	1607.27 1579.16	1607.30 1579.05	1607.26 1578.92	1607.39 1579.09
Aromatic mono substituted c-h deformation	702.69	702.83	702.78	702.79
C-H stretching of cycloalkanes	2930.45	2930.29	2929.90	2930.25

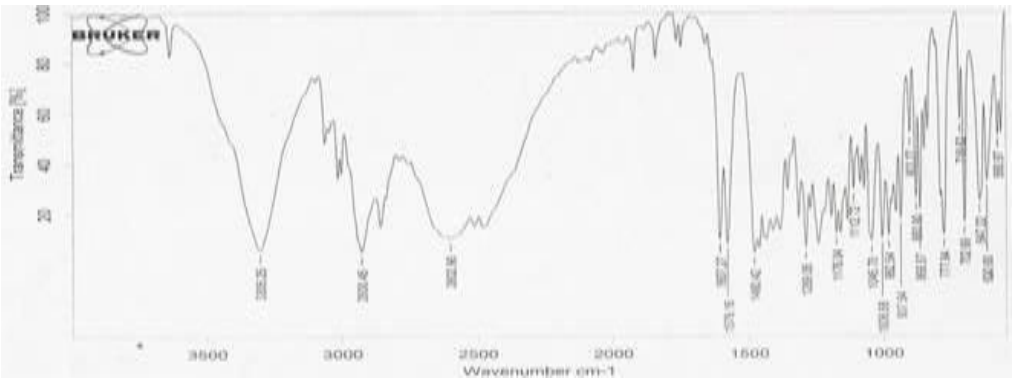

Fig No. 2: IR-Spectram of Tramadol Hydrochloride.

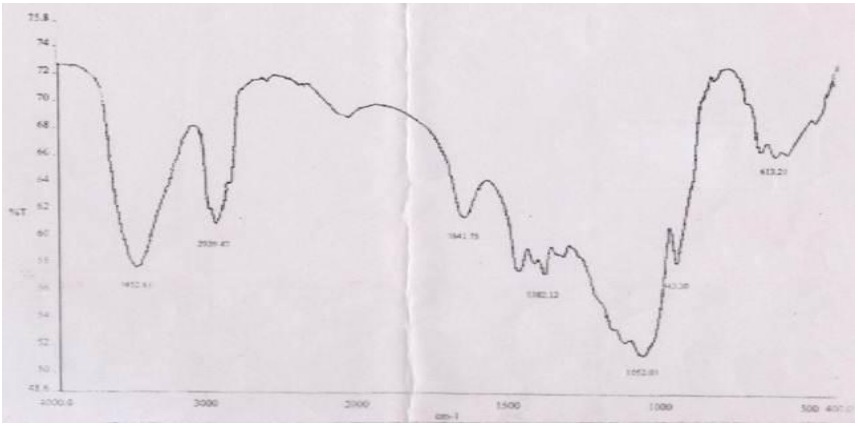

Fig No. 3: IR-Spectra of HPMC.

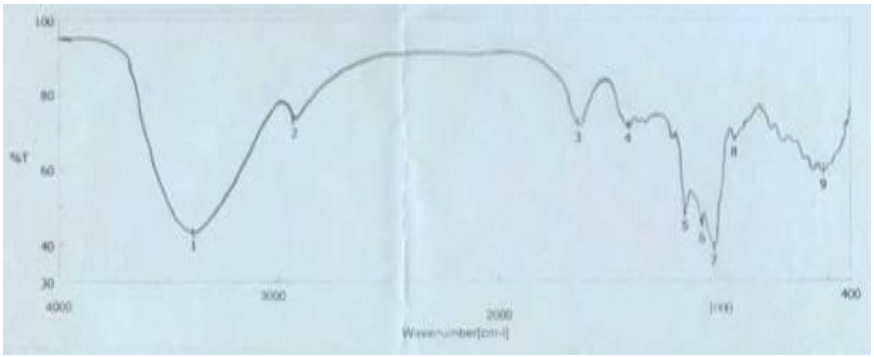

Fig. No 4: IR-Spectra of NaCMC.

Fig no. 5: IR-Spectra of Methyl Cellulose.

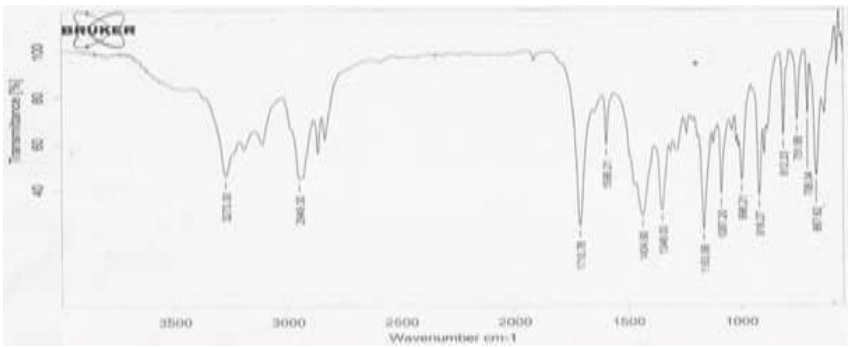

Fig no. 6: IR-spectra of physical mixture of Tramadol hydrochloride + HPMC.

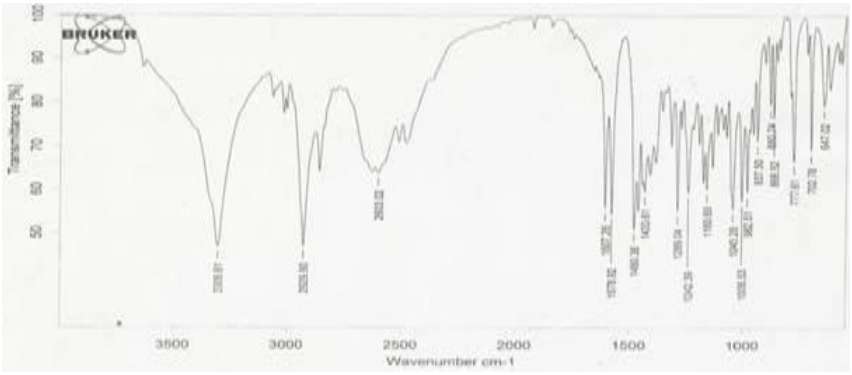

Fig no. 7: IR-spectra of physical mixture of trmadol hydrochloride + NaCMC.

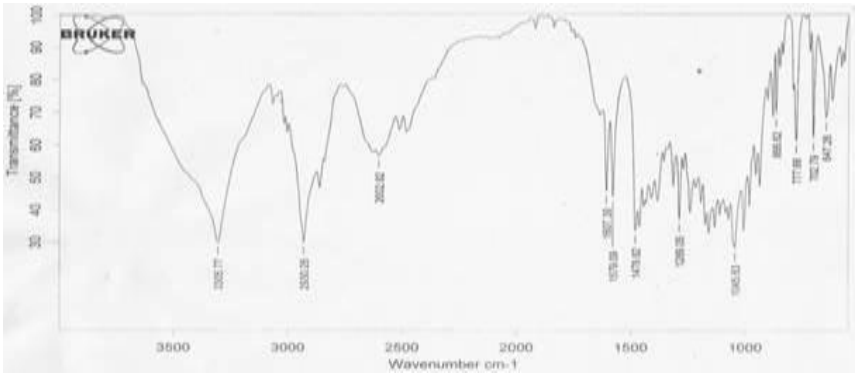

Fig no. 8: IR-spectra of physical mixture of trmadol hydrochloride + NaCMC.

Patient compliance is one of the important aspect for administration of drugs and attractive, taste masking, ease of administration are also needed to the patient. In the present study Tramadol Hydrochloride sweetened lozenges were designed and evaluated for effective treatment of pain in children. Drug-excipients compatability studies i. e Tramadol Hydrochloride and polymers (HPMC, NaCMC and MC) compatibility studies were conducted by using FT-IR spectral studies. The results of IR spectra of Tramadol Hydrochloride and polymers (HPMC, NaCMC, MC)individually and the physical mixture of Tramadol Hydrochloride and polymers (HPMC, NaCMC, MC) suggested that the characteristic peaks observed in Tramadol Hydrochloride pure samples were mostly identical with the peaks in the physical mixture of Tramadol Hydrochloride and polymers (HPMC, NaCMC, MC) adhering within their ranges without changes in the functionalities indicating their compatibility results given in table no 2 and fig 1, 2, 3, 4, 5, 6, 7 and 8. For formulation development drug excipient interactions play an important role so formulations were subjected to compatibility studies, so finally it was observed that there were no additional peaks in drug- polymer mixture and hence formulations were developed with the selected

polymers in the second stage of present investigations. Solution was filtered and suitably diluted. The drug content was estimated spectrometrically at 271 nm.

Table no. 4: INVITRO RELEASE DATA OF GLYCERO- GELATIN SOFT LOZENGES.

Time (min)	% DRUG RELEASE								
	F28	F29	F30	F31	F32	F33	F34	F35	F36
0	0	0	0	0	0	0	0	0	0
5	76.6± 0.01	76.2± 0.02	74.6± 0.03	74.6± 0.01	74± 0.01	73.3± 0.02	76.6± 0.03	76.2± 0.01	74.6± 0.021
10	89.4± 0.02	86.1± 0.02	81.6± 0.01	88.7± 0.04	83.5± 0.02	79.6± 0.01	88.1± 0.02	82.5± 0.02	80.3± 0.03
15	93.8± 0.04	91.2± 0.01	86.3± 0.04	93.8± 0.03	88.6± 0.03	84.5± 0.02	90.4± 0.04	86.9± 0.03	83.3± 0.02
20	82.6± 0.01	95± 0.04	87.4± 0.03	–	92.5± 0.04	87.8± 0.03	–	93± 0.04	87± 0.03
25	–	–	91± 0.01	–	–	91± 0.02	–	–	90± 0.03
30	–	–	94.4± 0.03	–	—	94.7± 0.04	–	–	93.8± 0.03
35	–	–	–	–	–	–	–	–	–
40	–	–	–	–	–	–	–	–	–
45	–	–	–	–	–	–	–	–	–

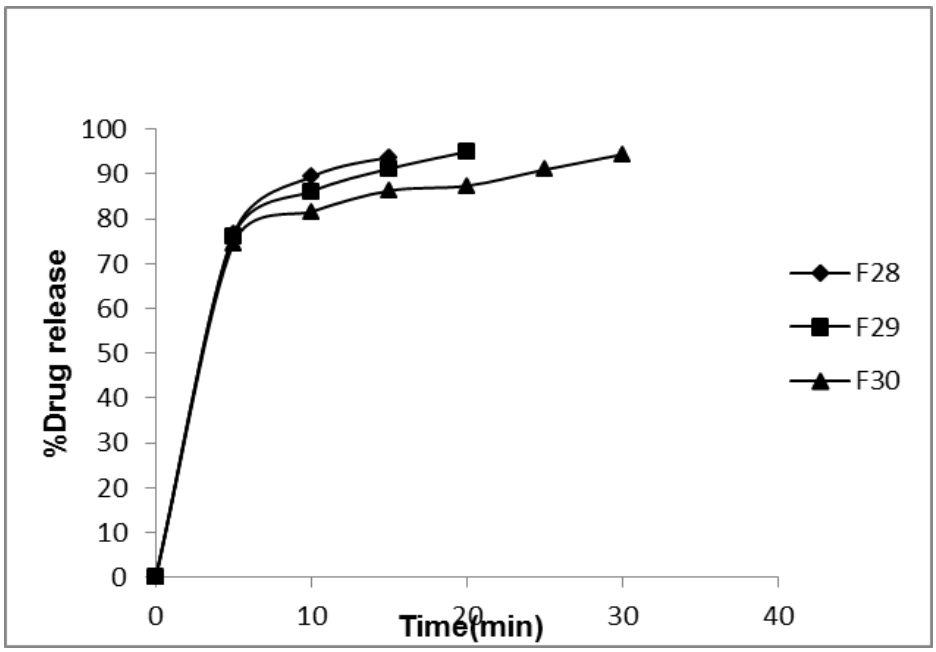

Fig no. 9: % Drug release plots of Soft lozenges Glycero-gelatin containing HPMC.

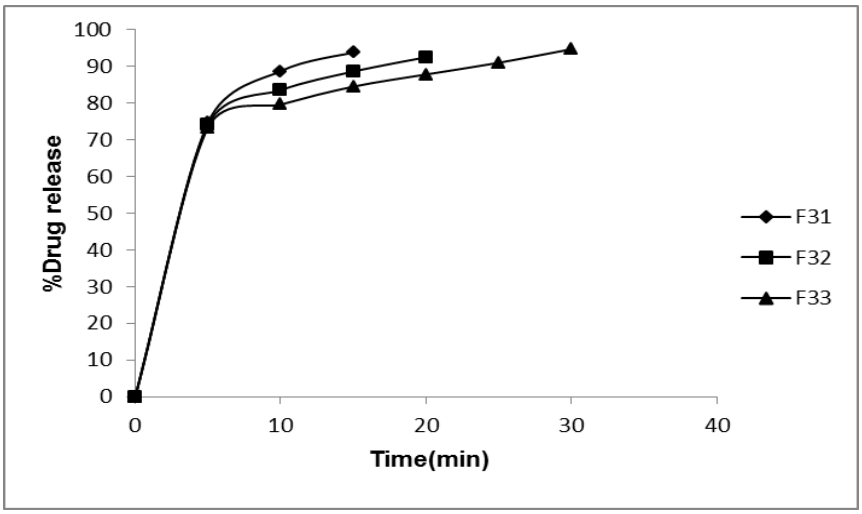

Fig no. 10: % Drug release plots of Soft lozenges Glycero-gelatin containing NaCMC.

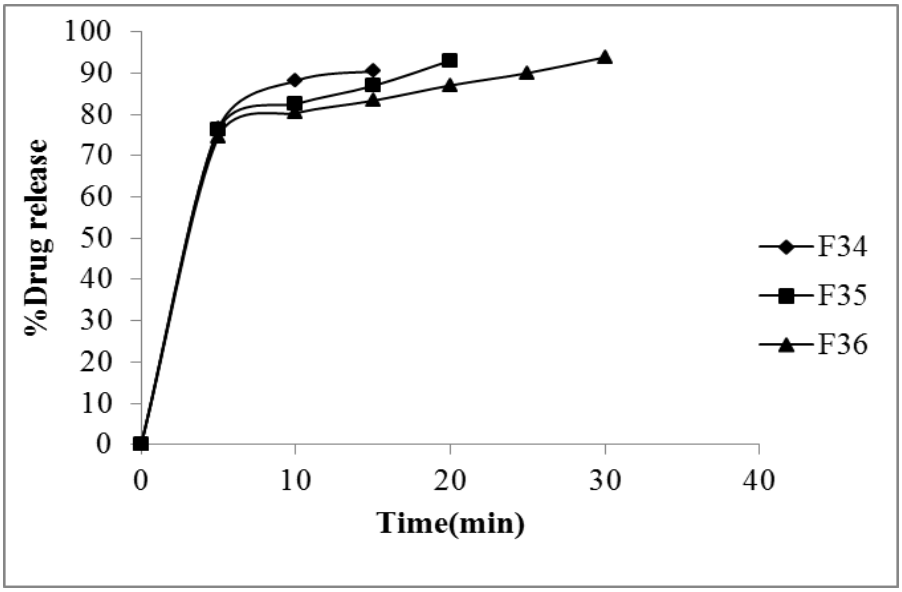

Fig no. 11: % Drug release plots of Soft lozenges Glycero-gelatin containing Methyl cellulose.

In the formulations mint flavour such as menthol are preferred in a slow dissolving lollipops, it provides a desirable soothing effect and by substantially micronizing or reducing the particle size of antacid salts were incorporated to improve the organoleptic properties including mouth feel and taste of the product. It yields a product exhibiting a dense, non-gritty and smooth texture for improved mouth feel. In order to enhance the flow of saliva an acidulate is employed in the dry mouth lollipops. These are generally present in amount ranging from about 0.1 to 0.5% by weight of lollipops.

Lollipops having wide advantages such as increase in bioavailability, reduce the gastric irritation, and to avoid the first pass metabolism. They can be prepared by molding (gelatin and / or fused sucrose or sorbitol base) or by compression of sugar- based tablets. Molded lollipops are sometimes referred to as troches. Molded lollipops have a softer texture because they contain a high percentage of sugar or a combination of a gelatin and sugar.

These lollipops are experiencing renewed popularity as a means of delivering different drug products, especially for patients who cannot swallow solid oral dosage forms and also used for it was designed for release of 30 mins for the treatment of pain in children's.

CONCLUSION

From the present study it was suggested that syrup based tramadol hydrochloride will be ideal dosage forms for the treatment of pain to the pediatrics. By incorporation of synthetic polymers yields good results and release the drugs for a prolonged period of 30 mines. Lollipops are intended to slowly dissolve in the mouth over a relatively long period of time. Eg; usually about 2-15 minsor more as needed. The taste bud and olfactory sences are able to detect even the slightest bittetness of unpleasant mouth feel and taste during such a long residence time in the mouth represents a substantial challenges it is desirable to provide a palatable dosage form of tramadol hydrochloride soft lollipops.

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