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Design and Fabrication of Oral Fast Dissolving Film of Tramadol Hydrochloride

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ABSTRACT: -

For the preceding two decades, there has been a heightened demand for more patient-compliant dosage forms. Modern progresses in the technology have offered viable dosage substitutions from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Buccal drug delivery has newly become a chief route of drug administration. Due to fast dissolution it afford sooner onset of action, sidestepping the first pass metabolism, dropping gastric degradation and metabolism of drugs and thus enhance their oral bioavailability. These properties of oral films with patient convenience and compliance made prevalent and accepted dosage form for pediatric and geriatric as well as adult residents.

Keywords: -Mouth dissolving film, Hydrophilic polymers, Formulation consideration, Manufacturing techniques, Evaluation parameters.

INTRODUCTION: -

The definitive aim of every drug conveyance system is the efficacious delivery of the drug, in which practically 90% of the drugs are directed to the body for the action of numerous sicknesses and disease as it is observed as the harmless, most suitable and most inexpensive method of drug delivery having the uppermost patient compliance. Fast dissolving oral films or oral wafers or oral strips or sublingual strips or oral thin films are the greatest forward-thinking form of oral solid dosage form due to more elasticity and coziness. [1] It progresses the usefulness of active pharmaceutical requirements by liquefying it within a minute of oral cavity after the interaction with saliva deprived of chewing and no necessity of water for administration. It provides speedy absorption and prompt bioavailability of drugs due to extraordinary blood flow and permeability of oral mucosa is 4-1000 times superior than that of skin. [2,3] Fast dissolving oral films are advantageous in patients such as pediatric, geriatrics, incapacitated, emetic patients, diarrhea, sudden period of allergic attacks or coughing for those who have an energetic life style. [4,5] The practice of such dosage form is likewise valuable whether indigenous accomplishment desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething. At present, Tramadol is accessible in the form of tablet, infusion as well as capsules in the market. Some pediatric and geriatrics patients are non-cooperative with these dosage forms. [6] From now oral disintegrating films have become important tool to improve the patient compliance.

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic binding to specific opioid receptors. It is castoff in the supervision of long-lasting pain and is suggested as chief line drug in the treatment of postoperative or orthopedic damage induced acute pain. The contemporary effort is planned to formulate and estimate oral fast dissolving film of tramadol hydrochloride as an innovative arrangement of continued analgesia for patients with orthopedic wounds. The drug possessions of tramadol hydrochloride are entirely appropriate on the drug selection criteria of the mouth dissolving film. Tramadol hydrochloride is fits to BCS class-I as it is having extraordinary solubility and high permeability which is tolerable for preparation of mouth dissolving film.

ANATOMY OF ORAL CAVITY: -

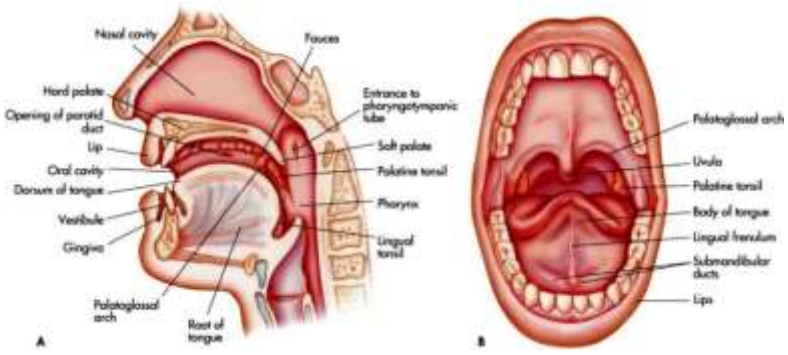


Fig 1:- Anatomy of oral cavity

The oral mucosa allows direct access of drug to the systemic circulation and avoids first pass metabolism. The permeability of oral mucosa is 4–1000 times greater than that of the skin. The oral mucosa is made up of an outermost layer of stratified squamous epithelium. Beneath this lines a basement membrane, alamina propia followed by submucosa as the innermost layer. Permeability coefficient of a drug is the measure of ease with which the drug can permeate a membrane. Order of permeability is intestine> buccal mucosa> skin. This permeability ranking is based upon the relative thickness and degree of keratinization 7.

MECHANISM OF ABSORPTION THROUGH ORAL MUCOSA: -

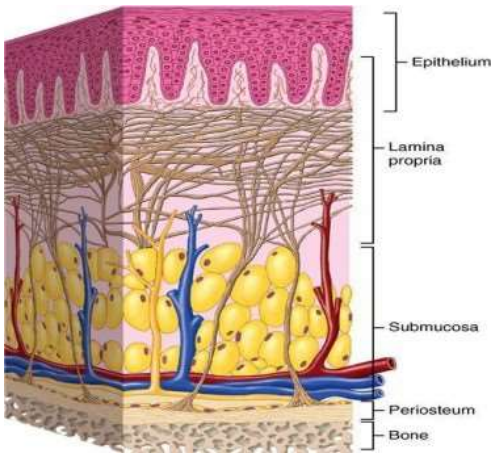


Fig 2: - Various layers of Epithelium

The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate, and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa and includes the buccal, sublingual, gingival, Palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue accounts for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells. The primary function of the oral epithelium is to protect the underlying tissue against potentially harmful agents in the oral environment and from fluid loss. Beneath the epithelium is the basement membrane, lamina propia, and sub-mucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue 8.

For passive drug transference, around two penetration passageways through the oral mucosa which are transcellular (intracellular, passing through the cell) and Para cellular (intercellular, passing around the cell). Drug fragment can use together of the track concurrently however one track is favored over the former depending upon physicochemical possessions of the drug. Cell membrane is lipophilic in nature and has trouble in permeation of hydrophilic solutes because of low partition coefficient. The lipophilic compounds are having little solubility in passive transport system because of the intercellular places which actions as an obstacle to permeation. Meanwhile the oral epithelium is stratified and solute permeation is convoyed by the amalgamation of these two itineraries. Hence, the route which has fewer amount of prevention to passage is favored over the other for permeation through oral mucosa 9.

MATERIALS AND METHODS: -

MATERIALS: -

The film forming polymer used was HPMC (Hydroxypropyl Methyl Cellulose) bought from Colorcon Asia private limited and pullulan received as a gift sample from RC patel college of pharmacy, Shirpur. Plasticizer used was commercial grade PEG 400 (Polyethylene glycol) purchased from Pallav chemicals and solvents private limited. The API used was Tramadol hydrochloride purchased from Balaji Drugs from Gujrat.

The method used was solvent casting method which seemed the most pragmatic approach to making oral films in laboratory setting. Other method like the hot melt extrusion technique is too complex to be performed in the laboratory.

METHODS: -

CHARACTERIZATION OF THE DRUG: -

Organoleptic properties: -

The powder was examined for the appearance (color, odor) and nature 10.

Melting point determination: -

The melting point of tramadol hydrochloride was evaluated by programmable melting point apparatus (Chemiline). The melting point was determined by introducing small amount of substance in capillary attached to apparatus. The drug sample was tested in temperature range 30oC-300oC and the point at which the drug melted was noted 11.

Determination of pH: -

The pH of tramadol hydrochloride in distilled water checked by using digital pH meter and reading was noted 12.

Ultraviolet spectroscopy: -

The samples were exposed to UV spectrophotometric analysis and were scanned for absorption maximum (λmax) in the range of 200-400 nm using UV spectrophotometer in a correct medium. The obtained data was compared with that of reference values in literature 13.

Compatibility studies: -

The infrared spectrum of tramadol hydrochloride (pure drug) was verified by potassium bromide dispersion procedure in which blend of drug and potassium bromide was positioned in the sample container and an infrared spectrum was verified using FTIR (Agilent Cary 630). The recognized peaks were equated with the principle peaks of the informed IR spectrum of tramadol hydrochloride and the sample was valid 14,15.

Formulation of placebo films: -

Polymers of single or in amalgamation were precisely weighed or liquefied in separate solvent and then casted in a petri dish. The films were permitted to dry overnight at room temperature.

Screening of polymer for film forming capacity: -

HPMC in addition to pullulan is famous for their decent film forming stuffs and has brilliant satisfactoriness. A number of natural and synthetic film forming polymer were used for the design of the film like sodium alginate, pectin, PVP K-30, gelatin etc. But, the faultless film formulation is achieved by HPMC E15 and Pullulan. Fabrication of film was done by using polyethylene glycol as a plasticizer and saccharin sodium was used as a sweetener 16.

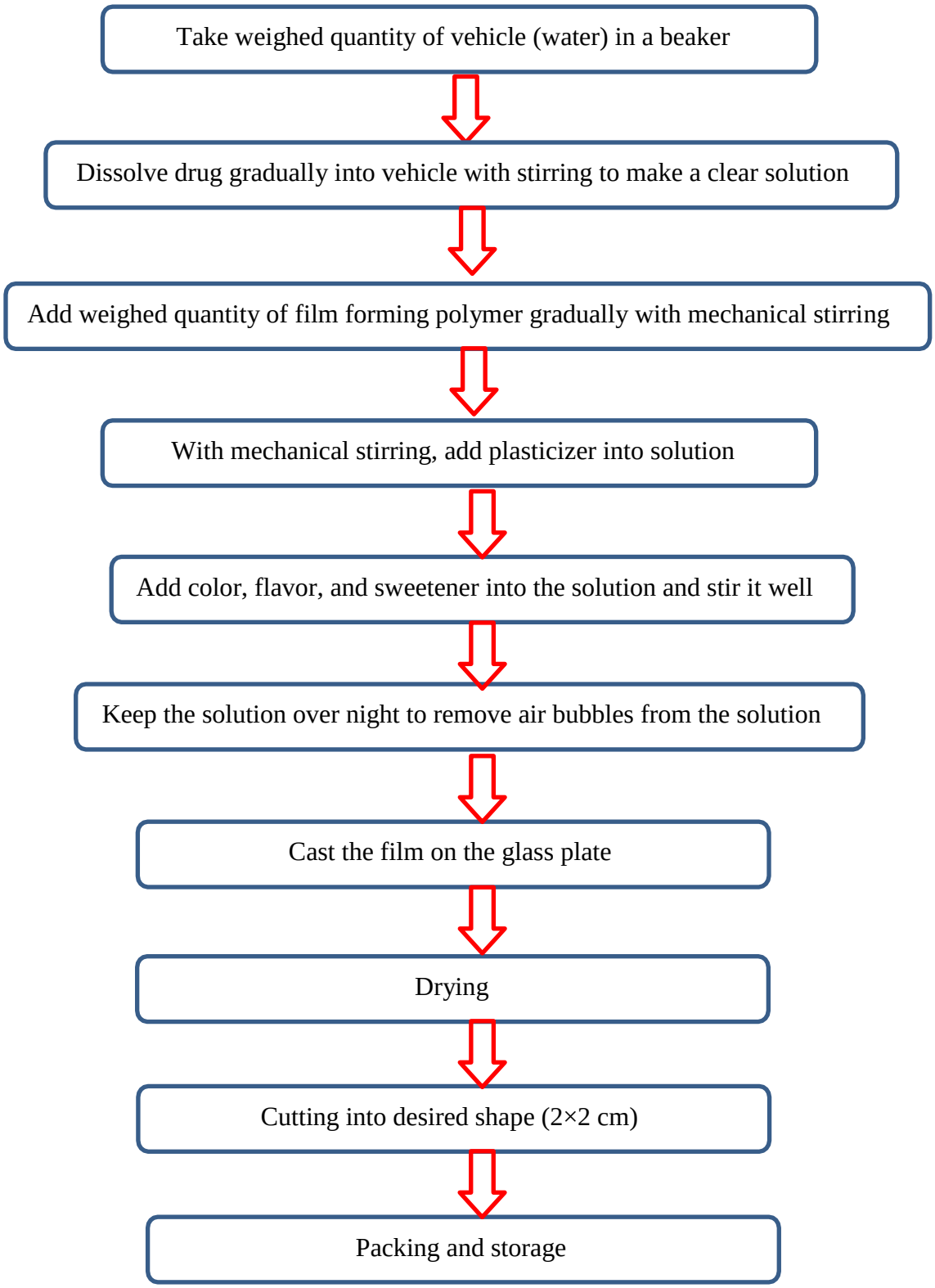
Preparation of drug loaded oral fast dissolving film: -

The fast dissolving films of tramadol hydrochloride were organized by solvent casting procedure. The fast dissolving films were equipped using different polymers like HPMC E15 and Pullulan. Polyethylene glycol used as plasticizer. The planned amount of polymer was spread in the solvent with nonstop stirring using magnetic stirrer and the homogenous solution is formed. The intended amount of drug resin complex (1:2) was fused in the polymeric solutions after involvement with required volume of plasticizer. Then the sweetener and flavor was added to drug mixed polymeric solution. Then the solution was reserved in sonicator for degassing. Then the bubble free solution was casted on to glass plate and was set aside in hot air oven. Dried film is then cut into the desired shape and size (2cm x 2cm) for the intended application 17,18.

Table 1: - Formulation of Tramadol Hydrochloride mouth dissolving film by solvent casting method

Formulation ingredients	**Formulation Code**							
	EK1	**EK2**	**EK3**	**EK4**	**EK5**	**EK6**	**EK7**	**EK8**
Tramadol hydrochloride (g)	0.937	0.937	0.937	0.937	0.937	0.937	0.937	0.937
HPMC E15 (%w/v)	1	1.5	2	2.5	…	…	…	…
Pullulan (%w/v)	…	…	…	…	1.5	2	2.5	3
Polyethylene glycol (%w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Citric acid (%w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium saccharin (%w/v)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Raspberry syrup	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Amaranth color	q.s	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	q.s

Chart: - Manufacturing procedure`s protocol for oral fast dissolving film



FORMULATION AND DEVELOPMENT: -

Screening of polymers for film forming capacity: -

1 2 3 4 5

Fig 18: - Screening of polymer concentration for film forming capacity

The pictorial appearance of the film was transparent and free from bubbles, which is obligatory for the aesthetic appeal of the film. Innumerable polymers like HPMC of different grades, PVP, sodium alginate, gelatin, pullulan were used and the resulted films were revealed in overhead figures. The above assessed parameters showed that HPMC E15, PVA and pullulan have preferred features like film forming capability and have decent visual appearance. The appearance of the film was establish to be transparent, semitransparent and the disintegration time was diverse acccording to the nature of the polymer. HPMC E15, pullulan based film formulations displays improved disntegration time as related to the other film forming polymers. So, HPMC E15 and pullulan were nominated as a film forming ploymer among all other polymer for further study.

Evaluation Parameters: -

Physical appearance and surface morphology: -

All arranged films exhibited good physical look and homogeneity without any flaws or imperfection. This parameter was examined by visual inspection of the film.

Weight Variation: -

The weight of the film was measured by cutting 2x2 cm2 size of the film at three altered places from the casted film and weight dissimilarity was measured. Weight of the film fluctuates from 47.6±0.05 to 63.0±0.12 mg. Thus from the result achieved it is perceived that as the concentration of the polymers are increasing, correspondingly the weight of film increasing**.**

Table 3: - Comparative evaluation of weight variation of mouth dissolving film

Sr. No.	Formulation code	Weight variation (Mean ±S.D.)
1	EK1	47.6±0.05
2	EK2	51.1±0.05
3	EK3	54.3±0.12
4	EK4	58.1±0.05
5	EK5	57.3±0.05
6	EK6	60.5±0.12
7	EK7	62.2±0.08
8	EK8	63.0±0.12

n=3, ±Standard Deviation (SD) In vitro disintegration time: -

Wholly the film revealed good disintegration time. Disintegration times of the films were increases as concentration of polymer increased. Formulation EK5 shows the slightest disintegration time likened to other films.

Table 4: - Comparative evaluation of in vitro disintegration time of mouth dissolving film

Sr. No.	Formulation code	Disintegration time (sec) (Mean ±S.D.)
1	EK1	52.05±0.02
2	EK2	70.23±0.05
3	EK3	66.56±0.03
4	EK4	33.44±0.05
5	EK5	20.99±0.02
6	EK6	28.73±0.04
7	EK7	62.36±0.08
8	EK8	37.56±0.05

n=3, ±Standard Deviation (SD) Thickness of the film: -

The thickness of the drug loaded film was measured by the assistance of digital vernier caliper. The EK5 had a minimum thickness and EK1 has a maximum thickness as compared with other formulation. The usual thickness of the film increased as soon as the concentration of the polymer increased and the molecular weight of the polymer. The result was displayed in table below.

Table 5: - Comparative evaluation of thickness of mouth dissolving film

Sr. No.	Formulation code	Thickness of the film (Mean ±S.D.)
1	EK1	0.17±0.008
2	EK2	0.18±0.005
3	EK3	0.20±0.008
4	EK4	0.21±0.005
5	EK5	0.15±0.005
6	EK6	0.16±0.008
7	EK7	0.18±0.005
8	EK8	0.19±0.005

n=3, ±Standard Deviation (SD)

Tensile strength and percent elongation of the film: -

Tensile strength of entire formulation was in acceptable range conceding that the films had good flexibility and mechanical strength. The outcomes were shown in table below. Percent elongation also contributes as an chief parameter in deciding the physical strength and flexibility of the film.

Table 6: - Tensile strength and percent elongation of the film

Sr. No.	Formulation code	Tensile strength(g/cm3)	Percent elongation (%) (Mean ±S.D.)
1	EK1	17.8±1.58	15.47±0.21
2	EK2	45.2±1.19	19.55±0.13
3	EK3	39.5±1.41	21.37±0.15
4	EK4	52.4±1.41	23.23±0.14
5	EK5	65.0±0.90	25.22±0.16
6	EK6	32.6±1.81	29.38±0.15
7	EK7	72.1±1.09	33.20±0.12
7	EK8	79.6±2.00	38.50±0.07

n=3, ±Standard Deviation (SD) Folding endurance of the film: -

It was measured manually. A strip of 2x2 cm2 was cut and exposed for the folding endurance studies until it disrupts at the similar place. It was found to be increased as soon as the concentration of polymer increased. The values of the films were shown below.

Table 7: - Folding endurance of the film

Sr. No.	Formulation code	Folding endurance
1	EK1	321±2.49
2	EK2	378±2.05
3	EK3	392±1.69
4	EK4	412±2.16
5	EK5	374±2.86
6	EK6	355±1.63
7	EK7	388±2.81
8	EK8	402±1.84

n=3, ±Standard Deviation (SD) Surface pH: -

The surface pH of all the formulations was taken with the help of pH meter. It was found to be near to the neutral pH signifying that there might be less possibility that will cause an irritation to the oral mucosa thus promoting patient acceptance.

Table 8: - Surface pH of mouth dissolving film

Sr. No.	Formulation code	Surface Ph (Mean ±S.D.)
1	EK1	6.78±0.02
2	EK2	6.75±0.01
3	EK3	6.65±0.02
4	EK4	6.83±0.01
5	EK5	6.50±0.01
6	EK6	6.67±0.02
7	EK7	6.72±0.02
8	EK8	6.50±0.01

n=3, ±Standard Deviation (SD) Swelling index: -

The measurement of swelling index specified that extreme swelling takes place in the formulation comprising advanced fraction of polymer. It affected release of the drug. Higher the percentage of the swelling index less the drug release.

Table 9: - Swelling index of mouth dissolving film

Sr. No.	Formulation code	Swelling index
1	EK1	0.063±0.0029
2	EK2	0.042±0.0032
3	EK3	0.042±0.0032
4	EK4	0.036±0.0029
5	EK5	0.033±0.0030
6	EK6	0.041±0.0019
7	EK7	0.053±0.0019
8	EK8	0.041±0.0032

n=3, ±Standard Deviation (SD) Drug content uniformity: -

The drug content uniformity assessment was achieved to ensure unvarying circulation of the drug. The ready formulations were scrutinized for the drug content uniformity and it was observed that all the drug content uniformity values lies between 98.6±0.56 to 99.6±0.23 which is tolerable within the limit as per USP-NF monograph of tramadol hydrochloride. The result indicated that drug was consistently dispersed in all the formulations as shown below.

Table 10: - Drug content uniformity of mouth dissolving film

Sr. No.	Formulation code	Drug content (%) ±S.D.
1	EK1	98.8±0.47
2	EK2	99.3±0.56
3	EK3	98.7±0.32
4	EK4	99.0±0.23
5	EK5	99.6±0.23
6	EK6	98.6±0.56
7	EK7	98.8±0.23
8	EK8	98.7±0.40

In vitro dissolution studies: -

Table 11: - In vitro dissolution data of mouth dissolving film formulation EK1 to EK8 in phosphate buffer pH 6.8 solution

Time	Cumulative percent drug released							
	EK1	EK2	EK3	EK4	EK5	EK6	EK7	EK8
0 sec	0	0	0	0	0	0	0	0
30 Sec	29.8±1.3 2	25.6±1.66	23.9±1.41	22.9±1.41	29.0±1.13	17.9±1.41	14.9±1.41	12.9±2.44
1 Min	46.6±1.41	29.7±1.27	29.7±1.27	29.7±1.27	38.0±1.41	27.9±2.32	22.9±1.41	17.9±1.41
2	56.4±1.6	41.0±1.13	30.7±2.32	30.7±2.32	53.2±1.13	31.7±2.60	30.3±2.0	28.8±1.27
Min	9							
4 Min	67.1±2.68	48.6±2.44	52.4±1.13	52.4±1.13	70.2±1.27	41.0±1.13	35.2±1.13	31.6±1.41
8 Min	79.1±1.55	59.4±1.27	64.3±1.41	64.3±1.41	79.1±1.55	49.6±1.41	50.4±1.69	45.4±2.44
10 Min	86.0±1.41	67.3±1.41	74.3±2.82	74.3±2.82	85.0±1.55	58.5±1.27	58.1±1.55	50.4±1.69
12 Min	92.1±1.50	84.3±2.44	76.1±1.55	76.1±1.55	88.2±1.27	69.3±2.40	65.1±1.28	58.1±1.55
15 Min	98.0±1.41	88.2±1.27	84.3±2.44	84.3±2.44	97.0±1.41	80.2±1.54	76.1±2.61	73.2±1.27

The in vitro drug release profile of entire formulations were familiarized into 900 ml of pH 6.8 phosphate buffer (dissolution medium) maintained at 37 ± 0.5 ºC with basket rotating at 50 rpm. Samples are reserved and analyzed spectrophotometrically using UV-Visible spectrophotometer. It was observed that every prepared film exhibited more than 70% of the drug release in 15 minutes. The study exposed that the drug release from the film covering HPMCE 15 as the polymer was more as compared to those containing pullulan. The reason behind higher drug release may be due to the lower viscosity of the polymer. Rapid drug dissolution was observed in formulation EK1, EK2, EK3 and EK5 which released 98.0, 97.0, 89.1, 88.2 percent respectively. Formulation EK5 shows higher drug release of 98.0 percent than other formulations. Slow drug release was observed in EK4, EK6, EK7 and EK8 with the release of 84.3, 80.2, 76.1 and 73.1 percent respectively at the end of 15 minutes.

The results showed that all the films showed r2 value range from 0.94 to 0.99 for zero order kinetics, 0.87 to 0.95 for first order kinetics, from 0.96 to 0.98 for Hixson Crowell model, from 0.97 to 0.99 for Higuchi model, from 0.97 to 0.99 for Korsemeyer–peppas equation. All formulation yielded a quality adjustment with zero order and first order kinetics. Higuchi plots were found to be linear with the correlation coefficient values of maximum (r2) 0.99. It was concluded that the release of the drug from the films followed the diffusion controlled mechanism. The release data when were fitted to Korsemeyer-peppas equation the release exponent values thus obtained was range from 0.29-0.42 (EK1-EK8) which follows Fickian diffusion and can be attributed to the rapid dissolution and erosion release mechanism.

Table 12: - In vitro drug release kinetics of formulation F1 to F6

Formulation Code	r2				
	Zero order	First order	Higuchi	Korsmeyar Peppas	Hixson Crowell
EK1	0.95	0.90	0.99	0.99	0.98
EK2	0.94	0.90	0.98	0.99	0.98
EK3	0.94	0.87	0.97	0.98	0.96
EK4	0.97	0.94	0.98	0.97	0.97
EK5	0.97	0.95	0.98	0.97	0.97
EK6	0.99	0.95	0.98	0.98	0.97
EK7	0.99	0.94	0.99	0.99	0.98
EK8	0.99	0.94	0.98	0.98	0.97

Stability studies

Stability study was achieved on the best formulation EK2 as per ICH guidelines for 60 days. Best formulation EK5 showed no chief changes and revealed that the best formulation was stable both at normal and accelerated conditions. The results for stability in accelerated conditions were depicted in table below.

Table 12: - Stability data of formulation EK5 at 40°C±2°C/75%±5% RH

Evaluation parameters	Initial	After 30 days	After 60 days
Appearance	Good physical appearance	Good physical appearance	Good physical appearance
Drug Content	99.6±0.23	99.03±0.68	99.06±0.32
Disintegration time(sec)	20.09±2	22.09±0.03	20.22±0.04
In vitro drug released	97.0±1.41	96.0±1.21	97.0±1.41

CONCLUSION: -

Mouth dissolving film is a better substitute to conventional oral dosage form as it has more patient compliance, particularly in pediatric and geriatric patients. The result achieved from the contemporary study clearly shows that finest formulation EK5 has sooner drug release within 15 minutes and has upgraded bioavailability by evading first pass metabolic effect. Taste masking of tramadol hydrochloride will have improved patient compliance. The present study shows that best formulation EK5 had decent physical, mechanical properties and stability. The present study concluded that mouth dissolving film of tramadol hydrochloride containing pullulan as a film forming polymer meet perfect requirements for fast release which can be a respectable mode to bypass extensive hepatic first pass effect and increase bioavailability. There is expectation for its scale up for commercialization and can be applicable to large scale production.

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