FORMULATION AND EVALUATION OF DEXTROMETHORPHAN LOADED POLYMERIC MICELLAR ORAL DISPERSIBLE TABLTES

P. Kavya[1], Pavankumar krosuri[1*]

Abstract
Dextromethorphan is a potent anti-tussive agent having low bio availability of 11%. The present research investigation was to prepare Polymeric micelles containing Dextromethorphan, nanotechnology-based drug delivery systems that enhance the solubility using different grades of Pluronic's F-68, F-188, F-407 respectively by solvent evaporation method. The Polymeric micelles so prepared were characterized for its particle size, Zeta potential, PDI, TEM analysis, Drug loading efficiency. Among various formulations PM9 showed greater drug loading efficiency i.e 90% and particle size of 50nm that will be further formulated into Oral Dispersible tablets using different super disintegrants like SSG, Cross povidone, Low- HPC, among various formulations F9 showed less disintegration time of 10 sec and maximum drug release of 98.89%. from the kinetic observations of optimized formulation F9, $R^2$of release data based on best curve-fitting method for selected ODT the drug release showed First order kinetics i.e R^2= 0.869 indicating that the drug release depends upon its concentration.

Keywords: Dextromethorphan, Polymeric micelles, nanotechnology, Oral dispersible tablets

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INTRODUCTION

A cough is body's way of responding when something irritates throat or airways. An irritant stimulates nerves that send a message to brain. The brain then tells muscles in chest and abdomen to push air out of lungs to force out the irritant. A cough is relatively painless, but it can be irritating and the effort of coughing can leave patient feeling achy and fatigued.An occasional cough is normal and nothing to worry about, but a cough that lasts for several weeks or more or one that produces discolored or bloody mucus may be a sign of a medical condition.Prolonged coughing can irritate the lungs and cause even more coughing. It is also exhausting and can cause dizziness or fainting, headaches, sleeplessness, urinary incontinence, vomiting, and even broken ribs.

The drug of choice in present research investigation is "Dextromethorphan", which is a cough suppressant.
For formulating this drug, we had chosen polymeric micelle which is a nano carrier in novel drug delivery system that shows advantageous of target the site of action and side effects may be eliminated etc.

Nanotechnology received a lot of attention with the never-seen-before enthusiasm because of its future potential that can literally revolutionize each field in which it is being exploited. In Drug delivery, nanotechnology is just beginning to make an impact. Many of the current "nano" drug delivery systems, however, are remnants of conventional drug delivery systems that happen to be in the nanometre range, such as liposomes, polymeric micelles, nanoparticles, dendrimers, and nanocrystals. Liposomes and polymer micelles were first prepared in 1960's, and nanoparticles and dendrimers in 1970's. Colloidal gold particles in nanometre sizes were first prepared by Michael Faraday more than 150 years ago, but were never referred to or associated with nanoparticles or nanotechnology until recently. About three decades ago, colloidal gold particles were conjugated with antibody for target specific staining, known as immunogold staining. Such an application may be considered as a precursor of recent explosive applications of gold particles in nanotechnology.

The importance of nanotechnology in drug delivery is in the concept and ability to manipulate molecules and supramolecular structures for producing devices with programmed functions. Conventional liposomes, polymeric micelles, and nanoparticles are now called "nanovesicles," and this, strictly speaking, is correct only in the nano size scale. Those conventional drug delivery systems would have evolved to the present state regardless of the current nanotechnology revolution. To appreciate the true meaning of nanotechnology in drug delivery, it may be beneficial to classify drug delivery systems based on the time period representing before and after the nanotechnology revolution.

There are several advantages of nano drug delivery systems over conventional drug delivery.

1. Optimum therapeutic- drug concentration in the blood or in tissue may be maintained over a prolonged period of time.
2. Pre-determined release rates of extended period of time may be achieved.
3. Duration for short half- life drug may be increased
4. By targeting the site of action, side effects may be eliminated.
5. Frequent dosing and wastage of the drug may be reduced or excluded.
6. Better patient compliance may be ensured.

NANO CARRIER FOR CONTROLLED & TARGETED DRUG DELIVERY

As the knowledge of the molecular biology and pathophysiology of diseases has expanded, more therapeutically précised and purpose specific drug are being developed. These newly developed drug has high potency (low therapeutic window) and required their localization of the particular site of their action. Most drugs are administrated by conventional immediate- release dosage forms. They distribute freely throughout the body & accumulate the non– specific organs in an undesirable manner and thus produce adverse side effects. To reduce these slides and increased their therapeutic benefits, they should be delivered to their respective site of action, and hence suitable carrier systems becomes mandatory requirement. Various novel carriers have been developed for the purpose. Among these colloidal carriers such as liposomes, nano- particles & supra molecular system, i.e., micelles have gained more attention in the field of controlled and targeted drug delivery. Recently new carriers such as inorganic particles, liquids crystal, aquasomes, carbon nano tubes, dendrimers etc. Are also investigated for the specialized purpose. In the following section, these carriers for the same purpose are brief.

Polymeric micelle:

In this present study, polymeric micelles are used as drug carrier. Polymeric micelles are the core-shell-type nanoparticle formed through the self-assembly of block copolymers or graft copolymers

in the selective solvents. Polymeric micelles are made up of a shell of hydrophilic polymeric blocks, such as poly ethylene glycol, and a hydrophobic polymer core such as poly propylene glycol.
Typical polymeric micelles have a spherical shape and the size is in the range of 10–100 nm. Compared with surfactant micelles, polymeric micelles show much higher thermodynamic and kinetic stabilities.They are mainly used to enhance the solubility of poorly soluble Drugs. The Drug used in the present Research Investigation is Detramethorphan which is having a low Bioavailability of 11% .By changing into polymeric micelles its solubility can be increased thereby increased Bioavailability may take palce.

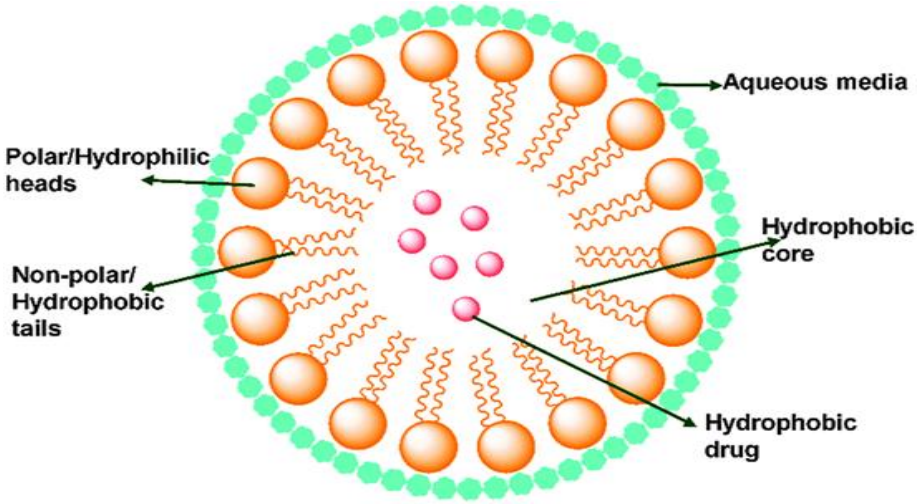


Fig.1

MATERIALS: Dextromethorphan, F-68,F-188, F-407, acetone sodium starch glycolate, cross povidone, low-substituted HPC, Micro crystalline cellulose, Magnesium stearate, Talc, Sucralose were obtained from KPlabs, Hyderabad.

METHODS:

Preparation of standard calibration curve of Dextromethorphan hydrochloride:

Accurately weigh 100mg of dextromethorphan hydrochloride and will be transferred into 100ml of volumetric flask. Suitable buffer (pH 6.8) will be added to dissolve the drug and the primary solution was made by adding the suitable solvent which is phosphate buffer 6.8 of 100ml which is 1000µg/ml. From this primary stock 10ml is transferred into 100ml of volumetric flask and make up the volume with the preferrable buffer pH 6.8 Sub concentrations of 2,4,6,8,10µg/ml respectively were prepared and analyzed for absorbance under UV-Visible spectrophotometer at a wavelength of 278nm, by following the above procedures and calibration curves will be plotted respectively.

FT-IR:

FTIR was performed to check the drug-excipient compatibility studies. The potassium bromide pellet technique was used in this investigation. The material was completely mixed with the dry powdered potassium bromide (KBr), then crushed with a dye to produce a disc. The disc was placed in the spectrophotometer and the spectrum was recorded over the wave number range of 3500cm^{-1}.

Preparation of Dextromethorphan Polymeric Micelles:

Polymeric micelles are prepared by using solvent evaporation method by following the steps mentioned below.

Step-1: The block copolymers and the drug were weighed accurately and transferred to a beaker

Step-2: To the above mixture add a sufficient quantity of volatile solvent which is Acetone to dissolve the above mixture.

Step-3: The completely dissolved solution is magnetically stirred at 600-800rpm for about 40min, there by obtaining a paste like mass which is dried further to get a solid mass.

These micelles were subjected to evaluation characteristics, the optimized formulation was selected and furtherly formulated into oral dispersible tablets by direct compression method with the use of different super disintegrants with different concentrations. The tablets were punched with the use of 8mm punch.

Table 1: Formulation table of Dextromethorphan Polymeric micelles:

Ingredients(mg)	PM1	PM2	PM3	PM4	PM5	PM6	PM7	PM8	PM9
Dextromethorphanhydrochloride	20	20	20	20	20	20	20	20	20
Pluronic F68	50	100	150	_-	-	-	-	-	-
Pluronic F188	-	-	-	50	100	150	-	-	-
Pluronic F407	-	-	-	-	-	-	50	100	150
Acetone(ml)	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml

Table 2: Formulation table of Dextromethorphan oral dispersible tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Polymeric micellear powder ≈20mg of Drug	170	170	170	170	170	170	170	170	170
SSG	6	8	10						
Crospovidone				6	8	10			
L-HPC							6	8	10
MCC	19	17	15	19	17	15	19	17	15
Mg. Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Sucralose	1	1	1	1	1	1	1	1	1
Total weight in mg	200	200	200	200	200	200	200	200	200

Evaluation of tablets:

General appearance:

Five tablets from all batches were randomly selected and organoleptic properties such as color, odour and shape were evaluated and data was represented.

Thickness:

The thickness for all the 5 tablets for all batches was measured using vernier calipers. The diameter was also determined by using vernier calipers. Thickness and diameter data was presented.

Hardness test:

Hardness of for five tablets for all the batches was tested using Monsanto hardness tester.. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and a zero reading is taken. The upper plunger is then forced against a spring by turning a thread Bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force, which is a measure of hardness.

Friability test:

The Roche Friabilator was used for this test, the device subjects as number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 RPM for 4 minutes by dropping the tablets from the distance of 6 inches with each revolution. Normally a pre weighed ten tablets are placed in the friabilator which is operated for 100 revolutions. The tablets are then dedusted and reweighed. A maximum loss of weight not greater than 1% present is acceptable for most tablets.

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

Weight variation test:

Weighed 20 tablets selected at random and calculated the average weight. Then percentage deviation from the average was calculated. According to IP standards, not more than two of the individual weight deviates from the average weight by more than the percentage shown in the table below, and none deviates by more than twice that percentage.

Table 3: IP standards of percentage of weight variation:

Average weight of tablet	%Deviation
80mg or less	10
More than 60mg but less than 250mg	7.5
250mg or more	5

***In vivo* Disintegration test:** This test is performed to ensure disintegration of tablets. One tablet is introduced into one tube of disintegration apparatus IP. The assembly suspended in beaker and containing distilled water and apparatus is operated until the tablet get disintegrated. The time taken for the complete disintegration of tablet is noted.

Taste evaluation:

Taste evaluation was done by panel of 6 volunteers, using time intensity method.1 tablet was held in

mouth for 10 seconds bitterness levels were recorded instantly and then at the end of 10 seconds, 30 seconds & 60 seconds. Bitterness levels are again noted and recorded.

Mouth feel test:
The same human volunteers participated in taste evaluation test, were asked give their opinion about the feeling of dosage form in the mouth and data was presented.

Water absorption ratio:
A folded piece of tissue paper was placed on tiny Petri dish holding 6ml of water. The time necessary for full wetting was measured using a tablet placed on the paper. The wetted tablet was then reweighed.

Water absorption ratio = final weight -initial weight*100/initial weight
Wetting time:
5 circular tissues of sheets of 10cm were put in a petri dish containing 6ml of solution of water-soluble dye methylene blue(w/v). A tablet was put gently on the surface. The time necessary for the color to develop on the upper surface of the tablet is referred to as wetting time.

Drug content uniformity test:
5 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100mg of drug was transferred to 100ml volumetric flask. small quantity of pH6.8 phosphate buffer is taken and sonicated for 30min. after sonication filter it and volume is adjusted with pH 6.8 phosphate buffer to 100ml.the concentration was diluted to 10µg/ml and absorbance was observed at 278nm.

***In vitro* drug release studies:**
In vitro dissolution study was performed in 9000ml pH6.8 phosphate buffer using USP type-2(paddle) apparatus at 50rpm for 30min (37±o.5°c). aliquots of the dissolution medium (5ml)were withdrawn at specific time intervals of 5,10,15,20,25,30 min. respectively and replaced immediately with equal volume of fresh medium. The samples were filtered and analyzed for drug content by measuring the absorbance at 278nm. The drug concentration was calculated and expressed as % drug released.

Kinetic studies:
Kinetic models were used for the study of release phenomenon of drug from dosage forms. Mathematically, it is easy to identify the designing of a particular pharmaceutical system and it can be used to predict the effect of device design parameters on the released kinetic of the formulation. It is easier to obtain the quantitative analysis of data for dissolution release rate by using these models. The choice of selection of best model/appropriate model depends on the desired or required productive ability and accuracy of the model. The underlying drug release mechanism can be elucidated which is not only of academic interest, but a pre-requisite for an efficient improvement of the safety of the formulation and for effective troubleshooting during production.

RESULTS:
Fourier transform infra-red spectroscopy (FTIR):

Fig.2: FTIR of pure drug

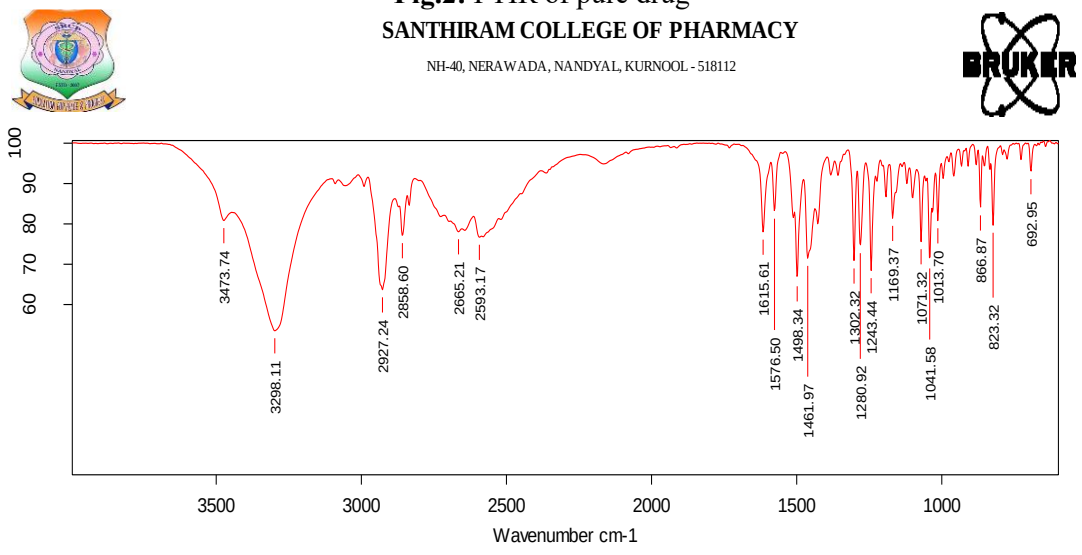


Fig.3: Construction of standard calibration values of Dextromethorphan hydrochloride 6.8 pH phosphate buffer

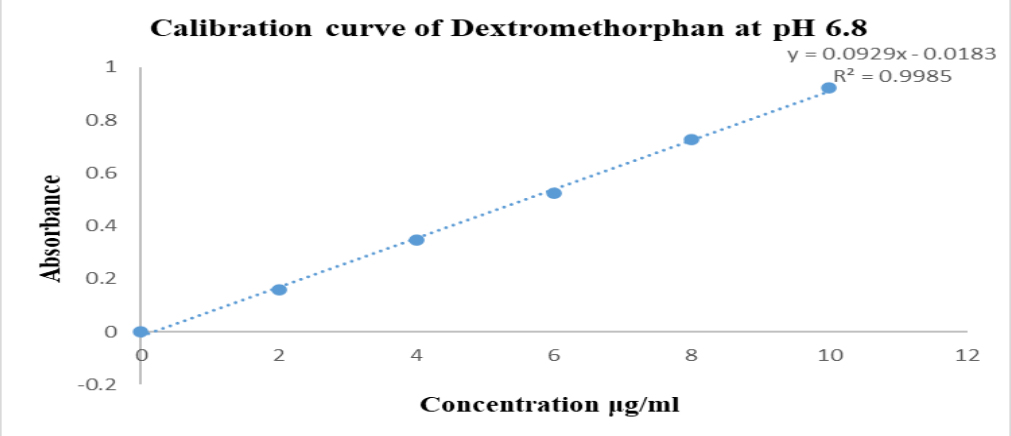
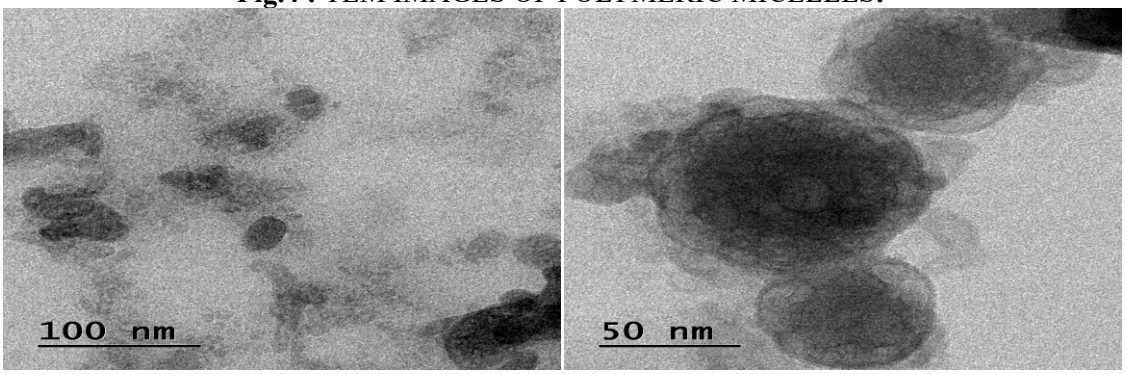


Table 4: Evaluation studies of Formulated Polymeric Micelles

Formulation Code	Particle size (nm)	Polydispersity Index	Zeta potential	%Drug loading Efficiency
PM1	150	0.52	-28.2	37.32
PM2	120	0.352	-24.4	45.35
PM3	100	0.321	-39.8	53
PM4	150	0.35	-27.8	56.25
PM5	100	0.346	-32.15	76.53
PM6	150	0.247	-31.2	78.25
PM7	200	0.312	-33.75	75.13
PM8	150	0.345	-52.35	80.21
PM9	50	0.245	-55	90

Fig.4 : TEM IMAGES OF POLYMERIC MICELLES**:**



EVALUATION PARAMETERS

Table 5: Pre-Compression parameters:

Formulation code	Bulk Density	Tapped Density	Hausners ratio	Compressibility Index	Angle of Repose(⁰)
F1	0.481	0.517	1.313	18.92	26.21
F2	0.513	0.498	1.299	19.21	23.53
F3	0.432	0.506	1.298	17.54	22.59
F4	0.326	0.596	1.276	17.04	27.23
F5	0.451	0.481	1.266	19.93	22.05
F6	0.394	0.603	1.193	21.15	26.54
F7	0.491	0.542	1.206	18.99	25.99
F8	0.513	0.498	1.299	19.21	23.53
F9	0.402	0.477	1.303	20.04	24.77

Table 6: Post Compression parameters

Formulation code	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	200	3.97	4.15	0.51
F2	200	3.23	4.12	0.68
F3	200	3.53	4.88	0.45
F4	200	3.98	4.96	0.49
F5	200	3.99	4.55	0.57
F6	200	4.03	4.17	0.31
F7	200	3.34	4.5	0.27
F8	200	3.71	4.48	0.44
F9	200	3.66	4.04	0.67

Table 7: Post Compression parameters

Formulation code	Wetting time (sec)	Water absorption ratio	*In-vitro* dispersion time(sec)	*In-vitro* disintegration time(sec)	Drug content %
F1	40	1.6	65	58	98.59
F2	35	1.8	63	55	97.55
F3	32	1.3	62	52	98.94
F4	26	1.8	63	53	98.86
F5	23	1.5	62	52	99.03
F6	22	1.8	61	49	99.06
F7	22	1.2	36	25	98.16
F8	16	1.3	33	20	98.53
F9	10	1.2	20	10	99.08

Dissolution parameters:

Table 8: Dissolution parameters for Prepared Formulation and Marketed Preparation

	% Cumulative Drug release									
Time (min.)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**Marketed Preparation**
0	0	0	0	0	0	0	0	0	0	0
5	35.78	50.54	53.45	50.35	52.85	58.51	52.58	53.23	74.38	53.23
10	43.45	52.34	54.21	56.32	58.38	60.83	68.83	58.52	80.66	58.35
15	46.36	55.58	65.35	64.58	64.86	68.36	73.35	63.12	85.34	63.21
20	48.35	65.68	73.89	67.31	72.35	75.35	80.55	73.32	88.56	68.13
25	50.76	66.35	75.83	73.58	75.28	80.57	84.35	83.85	92.53	73.83
30	53.06	72.3	78.85	79.57	80.31	83.1	84.35	90.63	98.89	83.85

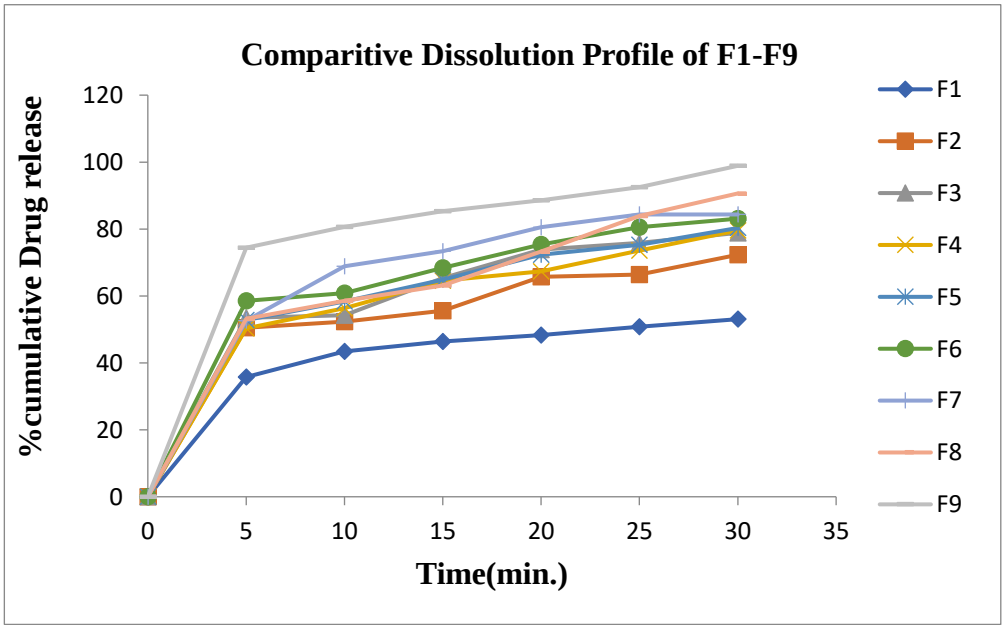


Fig.5

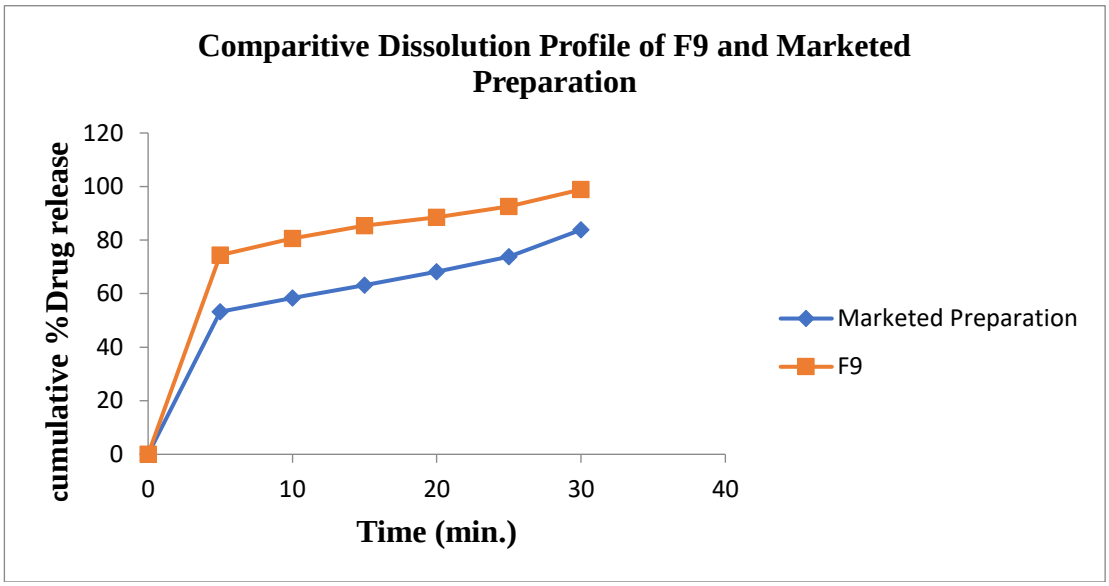


Fig.6

Table 9: Different Dissolution kinetic parameters of optimized formulation F9

Formulation code	Zero order R^2	First order R^2	Higuchi model R^2	Korsmeyer peppas R^2
F9	0.608	0.869	0.795	0.726

From the above observations Kinetic analysis (r^2) of release data based on best curve-fitting method for Dextromethorphan oral disintegrating tablets, the Drug release showed First order kinetics (R^2=0.869) indicated that the drug release depends upon its concentration.

CONCLUSION:

In the order to research investigation drug dextromethorphan belong to the category of anti-tussive having low bioavailability of 11% comes under BCS class-II,in order to improve its solubility drug was incorporated into polymeric micelles using different graded of Pluronic like F-68,F-188,F-407 by solvent evaporation method and were subjected to evaluation parameters like particle size, zeta potential, PDI drug loading efficiency .

Among different formulations PM9 shows high drug loading efficiency which will be furthered formulated into ODT for better patient compliance and therapeutic effect, the powder blend of thus formulated ODT were subjected into pre compression and post compression parameters. Among various formulations F9 showed a high %cumulative drug release of 98.89 which is even higher than marketed preparation i.e., 83.85%.

Kinetic studies were conducted for optimized formulation F9 from the kinetic studies R^2 value is more for first order kinetics i.e., R^2 0.869, indicating that the drug release depends upon its concentration.

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CONFICLICT OF INTEREST:

The authors declare no conflict of interest.

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