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FORMULATION AND EVALUATION OF FURAZOLIDONE MICROSPHERES

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ABSTRACT
The development of oral sustained or controlled release dosage form of Furazolidone has been an interested topic of research for a long period of time. Such drug is difficult to be delivered orally in a sustained or controlled release manner and, Due to its effectiveness and intensive use as a drug of choice in the treatment of cholera, colitis, and/or diarrhoea numerous sustained and controlled release formulations of Furazolidone have been made and reported. Furazolidone microspheres were prepared with a coat consisting of alginate and polymer such as HPMC and Sodium alginate by Ionic cross linking technique using CaCl2. The microspheres were evaluated with respect to the yield, particle size, incorporation efficiency, in vitro drug release and stability. Microspheres were characterized by FTIR studies. It was found that the particle size and incorporation efficiency of microspheres increases with increasing drug-to-polymer ratio.

KEYWORDS: Furazolidone, Ionotropic gelation technique, HPMC, Sodium alginate, FTIR studies, In vitro drug release studies.

INTRODUCTION
Novel drug delivery system has reached its pinnacle in last few years. Sustained drug delivery system is advantageous with its prolonged drug release mechanism which is desirable from the therapeutic point of view, for the treatment of chronic pain syndromes.[1] Microspheres are solid, approximately spherical particles ranging 1-1000 µm in size. They are made up of polymeric substances, in which the drug is dispersed throughout the microsphere matrix.[2] Microspheres can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time.[3] Furoxone has a broad antibacterial spectrum covering the majority of gastrointestinal tract pathogens including E. coli, staphylococci, Salmonella, Shigella, Proteus, Aerobacter aerogenes, Vibrio cholerae and Giardia lamblia. Furazolidone and its related free radical products are believed to bind DNA and induce cross-links. Bacterial DNA is particularly susceptible to this drug leading to high levels of mutations (transitions and transversions) in the bacterial chromosome.[4] Furazolidone microspheres used in the treatment of cholera, colitis, and/or Diarrhea caused by bacteria, and giardiasis.

MATERIALS
Furazolidone was obtained from Alkem Pvt Mumbai, Sodium alginate and HPMC were procured from SD fine chemicals Mumbai. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY
FT-IR Study
Drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for pure drug, polymer and drug-loaded microspheres using FTIR spectrophotometer (Jasco FTIR -410). Samples were prepared in KBr disks. The scanning range was 400-4000 cm-1 and the resolution was 2/cm.[5]

Formulation Table

Table 1: Formulation development of furazolidone microspheres.

F. No.	Furazolidone	Sodium alginate	HPMC	$Cacl_2$
F1	5	100	-	1%
F2	5	200	-	1%
F3	5	300	-	1%
F4	5	400	-	1%
F5	5	-	100	1%
F6	5	-	200	1%
F7	5	-	300	1%
F8	5	-	400	1%

Ionotropic gelation technique

In this method, polymers in different concentrations was dispersed in suitable solvent solution and homogenized for 1hr. Drug polymer solution was prepared by dispersing the drug (50 mg) slowly into previously prepared polymers slurry in different ratios with continuous and uniform stirring for 3 hr. A gelation medium was prepared separately by dissolving different percentages of calcium chloride in distilled water. Bubble free dispersion medium was extruded through glass syringe (20 Guaze) into the gently agitated calcium chloride solution. The agitation was carried out by mechanical stirrer at different rpm. Microspheres were separated by filtration from the solution, washed with water and dried.[6]

Evaluation of microspheres

Particle size analysis

Particle size was determined by using an optical microscope under regular polarized light and the mean particle size was calculated by measuring 50-100 particles with the help of a calibrated ocular micrometer.[7]

Morphological Characterization using SEM

The surface morphology of the microspheres was recorded with JEOL Scanning Electron Microscope (Model: JSM 5200). The samples were mounted on an Aluminium stub by using a double-sided adhesive tape. Then it was placed in an ion coater unit (Model: IB-2, Hitachi, Tokyo, Japan) for gold coating (200A). During gold coating process the sample were exposed to vacuum of 10-50 mm. After wards, a 50 accelerating voltage of 5 kV was applied and the image was photographed by Asia Pentex camera of 35 mm film.[8]

Drug entrapment efficiency

Taken 100 mg of chitosan microspheres and the amount of drug entrapped was estimated by crushing the microspheres and extracting drug into 100 ml methanol. After 24 hr, the extract was transferred to a 100 ml volumetric flask and the volume was made up using methanol. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically at 255 nm for Furazolidone respectively against methanol as a blank.[9] Then practical drug content was calculated from respective calibration curves. Percent drug entrapment efficiency was calculated using the following equation.

Drug entrapment efficiency (%) = Practical Drug content /Theoretical Drug content X 100

Percentage yield

The relative yield was calculated based on the amount of microspheres of each formulation obtained relative to the amount of solid materials used in the dispersed phase.[10] The percentage yield was calculated according to the following equation:

Percentage Yield (%) = Actual weight of microspheres /Total weight of drug and polymer X 100

In-Vitro drug release studies

In-vitro dissolution test was conducted in USP type 2 apparatus. 1 g of polymeric microspheres were taken and dissolution was performed at 50 rpm and at temperature of 37±0.5°C. Initial drug release studies were conducted in 900 ml of 0.1N HCl for 2 hr followed by 900 ml of pH 7.4 buffer solution for next 8 hr. Samples were collected at different time intervals filtered and assayed by UV spectrophotometry at 255 nm for Furazolidone respectively. The concentration of each sample was determined from a predetermined calibration curve for Furazolidone drug.[11]

Kinetics of drug release studies[12]

The quantitative elucidation of the values obtained in the dissolution study is facilitated by the usage of a generic equation that mathematically translates the dissolution curve in function of some parameters related to the microspheres. For understanding the mechanism of drug release and release rate kinetics of the drug 45 from dosage form, the Invitro drug dissolution data of optimized formulations obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix and Korsmeyer-Peppas models.

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

$Q0 - Qt = K0t$

Arrangement of equation yields: $Qt = Q0 + K0t$

Where Qt is the amount of drug dissolved in time t,

Q0 is the initial amount of drug in the solution (most times, Q0 = 0)
and K0 is the zero-order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time.

First order kinetics
The equation for first order release is given below
Log Qt = log Q0+ K1t/2.303
Where Qt is the amount of drug released in time t,
Q0 is the initial amount of drug in the solution
and K1 is the first order release constant.

A graph of the decimal logarithm of the released amount of drug versus time will be linear. Microspheres following this dissolution profile release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model
Higuchi described drug release as a diffusion process based on the Fick's law, square root time dependent. The simplified Higuchi equation is represented as
Qt=Kt ½
Where Qt = amount of drug released in time t,
K = Higuchi's constant

A linear relationship between amount of drug released (Q0 versus square root of time (t½) is observed if the drug release from the microspheres is diffusion controlled.

Korsmeyer-Peppas Model
This mathematical model, also known as the Power Law, has been used, very frequently; to describe the drug release from several different pharmaceutical modified release dosage forms. The Korsmeyer-Peppas model relates drug release exponentially to time. It is described by the following equation
Mt/M∞ = atn

Where 'a' is a constant incorporating structural and geometric characteristics of microspheres, 'n' is the release exponent, indicative of the drug release mechanism, and the function of 't' is Mt/ M∞ (fractional release of drug).

Stability studies[13]
Once the delivery system was developed, the practical utility of the formulation depends on the maintenance of the therapeutic efficacy throughout the shelf-life under different storage conditions. Various In vitro characterization parameters (physical appearance, entrapment efficacy, and drug release) of the microspheres were assessed after storage of the best formulations for 3 and 6 months at 40±2oC/ 75±5% RH according to ICH guidelines, and results were compared with those obtained before storage.

RESULTS AND DISCUSSION

Drug - Excipient Compatibility Studies (FT-IR)
The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug and polymer.

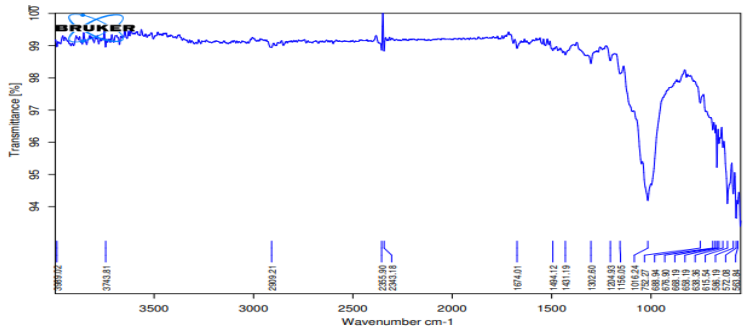

Fig. 1: FT-IR Sample for Pure Drug.

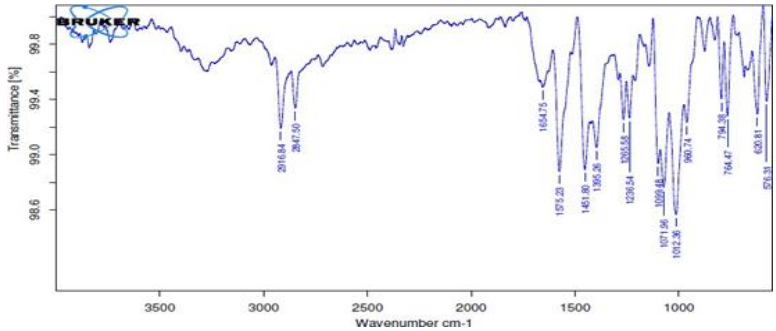

Fig. 2: FT-IR Sample for Physical Mixture of Drug and Excipients.

Formulation and Evaluation of sustained release microspheres of furazolidone

Optimization of formulation variables

Therefore, the optimized conditions for the formulation of sustained release microspheres were:

Results of the evaluation parameters of formulated sustained release microspheres

The prepared sustained release microspheres were evaluated for various parameters such as yield, drug entrapment efficiency, particle size, and in vitro drug release. And effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on particle size, yield, entrapment efficiency, and *in-vitro* release of cyclobenzaprine hydrochloride from sustained microspheres were also studied.

Characterization of microspheres

Surface Topography by Scanning Electron Microscopy (SEM)

Figure A shows SEM photograph of optimized microspheres at 100× magnification, at 1000× magnification. SEM photographs showed discrete, spherical microspheres. SEM photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface**.** The drug crystals on microspheres were may be due to the presence of un entrapped drug in dispersion medium.

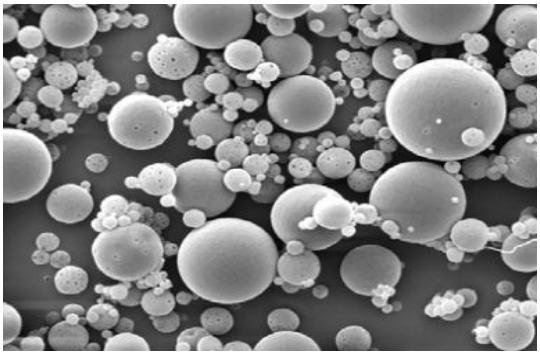

Fig. 3: SEM Photograph.

Effect of formulation and process variables on Yield of sustained release microspheres, Particle size, Drug entrapment efficiency

Table 2: Effect of drug polymer ratio on Yield of microspheres, Particle size, Drug entrapment efficiency.

Formulation Code	% yield	Particle Size	Drug Entrapment Efficiency
F1	76.80	403	82.39
F2	75.58	396	80.94
F3	79.53	425	84.56
F4	75.21	430	83.14
F5	74.39	415	78.91
F6	69.56	423	76.42
F7	65.85	418	75.41
F8	70.27	431	74.85

Drug release studies

Table 3: *In Vitro* Release Data of Microspheres F_1 to F_8.

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	13.69	14.96	15.98	14.46	13.98	10.25	14.93	13.65
2	27.96	29.68	30.42	25.89	24.51	26.37	28.92	27.84
3	33.58	32.54	40.25	35.75	34.93	32.54	31.54	30.49
4	43.50	45.89	50.12	42.24	43.52	40.17	48.96	47.82
5	52.90	53.64	62.32	59.52	57.81	55.58	58.90	57.42
6	63.89	65.81	75.25	72.41	68.82	67.95	68.52	67.98
7	76.98	77.42	82.96	80.43	81.42	82.31	79.87	78.58
8	90.25	92.35	95.82	93.25	92.20	93.53	94.50	92.55

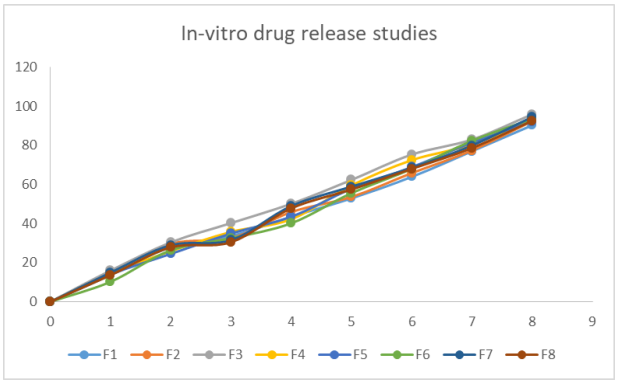

Fig. 4: In Vitro Drug Release of (F1- F8) Formulation.

Drug release kinetics

All the 8 formulation of Furazolidone microspheres prepared were subjected to in vitro release studies these studies were carried out using Franz diffusion cell apparatus.

The dissolution medium consisted of 10 ml of Standard buffer pH 7.4 period of time.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

- Cumulative percent drug released vs. time (zero order rate kinetics)
- Log cumulative percent drug retained vs. time (First Order rate Kinetics)
- Cumulative percent drug released vs. square root of time (Higuchi's
- Classical Diffusion Equation)
- Log of cumulative % release Vs log time (Peppas Exponential Equation)

Table 4: Drug Release Kinetics of Formulation F3.

TIME	%CDR	SQARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0	0	0	0	0	0	0
1	15.98	1	0	1.20357677	84.02	1.92438268
2	30.42	1.41421356	0.30103	1.48315921	69.58	1.84248442
3	40.25	1.73205081	0.47712	1.60476588	59.75	1.77633791
4	50.12	2	0.60206	1.70001106	49.88	1.69792644
5	62.32	2.23606798	0.69897	1.79462744	37.68	1.57611089
6	75.25	2.44948974	0.77815	1.8765065	24.75	1.3935752
7	82.96	2.64575131	0.8451	1.91886874	17.04	1.23146959
8	95.82	2.82842712	0.90309	1.98145617	4.18	0.62117628

Zero order kinetics

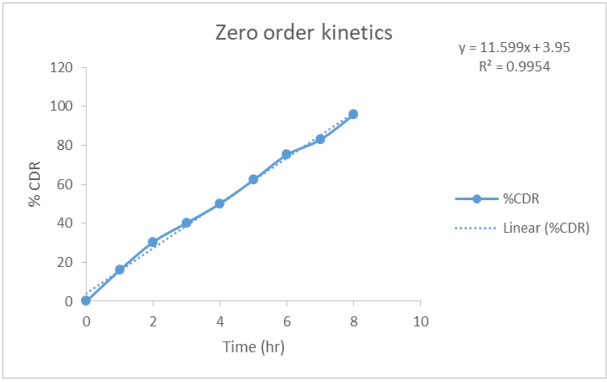

Fig. 5: Zero order kinetics of optimized formulation.

First order kinetics

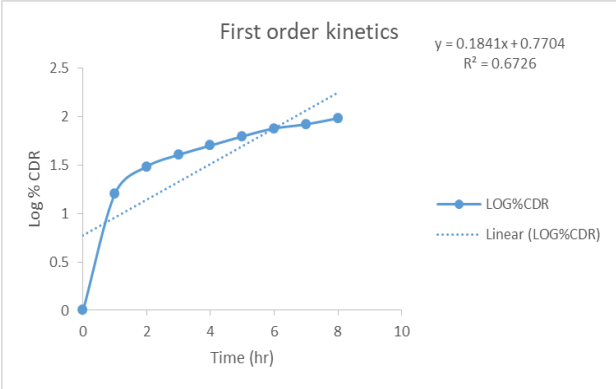

Fig. 6: First order kinetics of optimized formulation.

Higuchi model

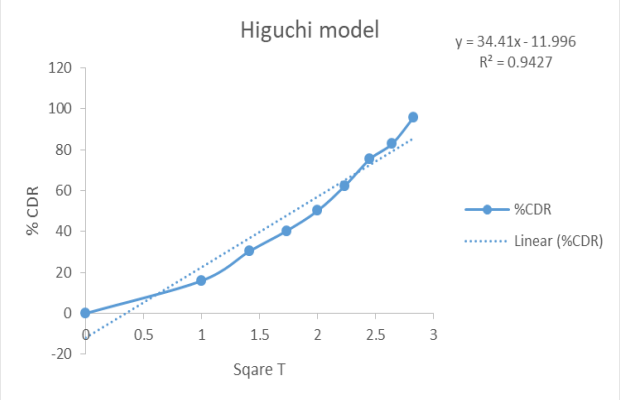

Fig. 7: Higuchi model of optimized formulation.

Korsmayer peppas

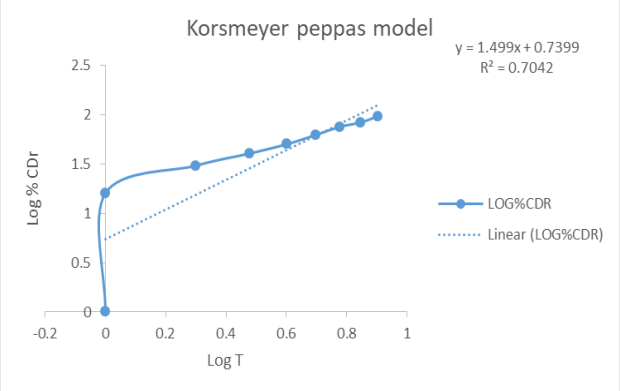

Fig. 8: Korsmayer peppas of optimized formulation.

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix, Peppas were respectively.

Regression values are higher with Zero order release kinetics. Therefore all the Furazolidone microspheres Zero order release kinetics.

The table indicates that r^2 values are higher for Higuchi's model compared for all the formulation. Hence Famotidine release from all the buccal films followed diffusion rate controlled mechanism.

Stability studies

There was no significant change in physical and chemical properties of the Microspheres optimized formulation after 90 days. Parameters quantified at various time intervals were shown;

Table 5: Results of stability studies of optimized formulation.

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	25^0C/60%RH % Release	95.82	94.58	93.65	92.82	Not less than 85 %
F-3	30^0C/75% RH % Release	95.82	94.62	93.52	92.37	Not less than 85 %
F-3	40^0C/75% RH % Release	95.82	94.50	93.45	92.58	Not less than 85 %

CONCLUSION

Attempt has been made to prepare sustained release microspheres of Furazolidone. These microspheres are used to treatment of cholera. The microspheres were prepared by Ionotropic gelation technique method using natural polymers as retarding polymers and evaluated for parameters like percentage yield, particle size, entrapment efficiency and the effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on evaluated parameters. Microspheres morphology was evaluated by SEM.

The yield and entrapment efficiency was high for Sodium alginate microspheres were Particle size, entrapment efficiency and production yield were influenced by the type of polymer, polymer concentration, stirring speed and combination of polymers. *In vitro* diffusion of optimized formulations of various Polymers in pH 7.4 formulations are releasing the drug up to 8 hrs.

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