FORMULATION AND EVALUATION OF HYDROGEL BEADS OF DRONEDARONE

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Abstract

The present study consists of formulation and evaluation of Hydrogel Beads of Dronedarone. Hydrogels are polymeric networks that take in and keep huge quantities of water. There are hydrophilic groups in the polymeric network which become hydrated in aqueous media thus forming hydrogel structure. The main objective of the present work was to evaluate the formulation of Hydrogel beads of Dronedarone. Preformulation studies like solubility and UV analysis complied with standards. The FTIR Spectra revealed that, there was no interaction between Dronedarone and polymers. From the results it can be inferred that there was a proper distribution of Dronedarone in the beads and the deviation was within the acceptable limits. The study also indicated that the amount of drug release decreases with an increase in the polymer concentration. The *in vitro* performance of Dronedarone Hydrogel beads showed prolonged and controlled release of drug. The *in vitro* dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order, first order and Higuchi and korsemeyer-peppas equation. Optimized formulation F12 shows r^2 value 0.974. As its value nearer to the '1' it is conformed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot. The 'n' value is 1.021 for the optimized formulation (F12) i.e., n value was >0.89 this indicates Super case transport.

Keywords: Hydrogel, Dronedarone, polymer, korsemeyer-peppas equation.

Introduction

Hydrogels are polymeric networks that take in and keep huge quantities of water. There are hydrophilic groups in the polymeric network which become hydrated in aqueous media thus forming hydrogel structure. Hydrogels were first reported by Wichterle and Lím. By definition, water must constitute at least 10% of the total weight (or volume) for a material to be a hydrogel. Hydrogels also possess a degree of flexibility very similar to natu- ral tissue due to their significant water content [1].

However, in most cases such conformational transitions are reversible; therefore, the hydrogels are capable of returning to their initial state after a reaction as soon as the trigger is removed [2]. The response of hydrogels to external stimuli is mainly determined by the nature of the monomer, charge density, pendant chains, and the degree of cross-linkage. The magnitude of response is also directly proportional to the applied external stimulus. Support of suspended cell populations prior to injection, throughout the solidification process, and within the lesion site. Cellular therapies are more effective when delivered and maintained locally in the injured area as opposed to being delivered systemically [3]. The importance of design parameters is originating from the difficulty in isolating the effects of cross-linking and macromer concentration-dependent material properties such as mechan-ical stiffness, mesh or pore size, degradation rate, and bioactive ligand density [4].

Hydrogel beads

Hydrogels beads are three-dimensional, cross-linked networks of hydrophilic polymers formed in spherical shape and sized in the range of 0.5–1.0 mm of diameter. Beads are formed by various cross-linking methods such as chemical and irradiation methods. Natural polymer-based hydrogels are biocompatible and biodegradable and have inherently low immunogenicity, which makes them suitable for physiological drug delivery approaches. The cross-linked polysaccharide-based hydrogels are environment-sensitive polymers that can potentially be used for the development of “smart” delivery systems, which are capable of control release of the encapsulated drug at a targeted colon site. This topic focuses on various aspects of fabricating and optimizing the cross-linking of polysaccharides, either by a single polysaccharide or mixtures and also natural-synthetic hybrids to produce polymer-based hydrogel vehicles for colon-targeted drug delivery [5].

Materials and equipments

Table 1: List of Materials

Ingredients	**Source**
Dronedarone	Aurovindo Pharma LTD, Hyderabad
Sodium Alginate	S.D. Fine Chem. Ltd. Mumbai.
Sodium CMC	S.D. Fine Chem. Ltd. Mumbai.
HPMC K4M	Himedia Laboratories Pvt. Ltd. Mumbai -
Carbopol	Finar Chemicals Ltd, Ahmedabad
Calcium chloride(%)	S.D. Fine Chem. Ltd. Mumbai.

Table 2: Details of the equipments used with manufacturer

S. No.	Instruments used	Source
1.	UV-Visible Spectrophotometer 2060 plus	Analytical Technologies Limited, Mumbai
2.	Electronic balance	Citizen CTG - 302
3.	P^H meter	Spectronics India PVT Ltd, Haryana
4.	Franz Diffusion cell	Lab India PVT Ltd, Mumbai
5.	Fourier-transformed Infrared Spectrophotometer	Bruker Pvt. Ltd, Germany
6.	Brook field viscometer	Kavin Scientific Products, Chennai
7.	Magnetic stirrer	Kavin Scientific Products, Chennai

Methodology

Preformulation study

Solubility study: The solubility test of Dronedarone was performed by using different solvents like water, methanol, ethanol, 0.1N HCL, 6.8P^H phosphate buffer [6].

Construction of calibration curve

Determination of λ max: A solution of containing concentration 2µg/ml was prepared with the distilled water and scanned with the help of UV- Visible spectrophotometer at the wave length of 200-400 nm. The maximum absorbance obtained in the graph was considered as **λ** max for the drug Dronedarone.

Preparation of stock solution: Accurately weighed amount of 10mg of Dronedarone was transferred into a 100ml volumetric flask. And the volume was made up to 100ml with 0.1NHCL. The resulted solution had the concentration of 100 mg/ml (1000µg/ml).This was labeled as stock solution-1.

Preparation of working standard solution: From above stock solution-I 10ml was taken and diluted to 100ml with 0.1N HCL which has given the solution having the concentration of 100 µg/ml. This was labeled as stock solution as stock solution-2.

Preparation of serial dilution for standard calibration curve: From stock solution-2 aliquots of 1, 2, 3, 4, 5, 6, 7ml were pipette into10ml volumetric flasks. The volume was made up with 0.1N HCL to get the final concentration of 9, 8, 7, 6, 5, 4, 3µg/ml respectively.The absorbance of each concentration was measured λ max at 232nm by using double beam UV-Visible spectrophotometer. Standard graph was plotted between concentration (on x-axis) and absorbance (on y-axis). This preformed in triplicate to validate the calibration curve [7].

FTIR study: Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy) in order to confirm that the entrapment of drug within the polymeric systems involves only the physical process and no interaction persists with drug and polymer combination. FTIR absorption spectra of pure drug, all the polymers used, and the combination of drug and polymers were taken to confirm the identity of the drug and to detect the interaction of the drug with the excipients [8].

The compatibility of the drug in the formulation was confirmed by FTIR spectral analysis. FTIR spectra of Dronedarone and formulation containing all polymers were determined by using the shimadzu FT-IR 8300 spectrophotometer by potassium bromide pellet method in the wavelength region of 4,000 to 400 cm^{-1}. The procedure consisted of dispersing a sample in potassium bromide and compressing into discs by applying a pressure of five tons for five minutes in a hydraulic press. The pellet was placed in the light path, and the spectrum was obtained.

Formulation of Hydrogel Beads:

The method used for preparation of hydrogel beads is Ionotropic gelation method. Accurate quantity of polymer was dissolved in 25ml of distilled water and stirred to form dispersion. Drug was added to the above dispersion and again stirred for uniform distribution and stirred until a homogenous mixture was obtained. The mixture was extruded through a 23G syringe needle into calcium chloride solution (1% w/v). The beads were allowed to remain in the same solution for 30 min to improve their mechanical strength [9]. The formed beads were separated, washed with water and allowed to dry at room temperature overnight.

Table 3: Formulation Design for Dronedarone hydrogel beads

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Dronedarone	150	150	150	150	150	150	150	150	150	150	150	150
Sodium Alginate	150	300	450	600	150	300	450	600	150	300	450	600
Sodium CMC	150	300	450	600	-	-	-	-	-	-	-	-
HPMC K4M	-	-	-	-	150	300	450	600	-	-	-	-
Carbopol	-	-	-	-	-	-	-	-	150	300	450	600
Calcium chloride (%)	2	2	2	2	2	2	2	2	2	2	2	2

Evaluation of Hydrogel Beads

Surface Morphology (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope. Dry Dronedarone gel beads were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of Dronedarone hydrogel beads were taken by random scanning of the stub [10].

Percentage Yield

Percentage practical yield of Dronedarone hydrogel beads was calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Dronedarone beads recovered from each batch in relation to the sum of starting material. The percentage yield of Dronedarone beads prepared was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug Content

To determine the drug content and encapsulation efficiency of the beads, 40 mg beads were crushed using a porcelain mortar and a pestle, and dispersed in suitable solvent. The dispersion was sonicated for 15 minutes and left overnight for 24 hrs, then the dispersion was filtered. A 1 ml sample was taken and diluted with suitable solvent, and drug content assayed using a UV-visible spectrophotometer at λmax of 232 nm . The drug content of each formulation was recorded as mg / 200 mg of gel beads.

Drug Entrapment Efficiency

The drug entrapment efficiency of prepared beads was determined by using the following equation [11].

EE (%) = Actual Drug Content/ Theoretical Drug Content X 100

In-vitro dissolution studies

Procedure for In-vitro dissolution study

The release rate of Dronedarone Hydrogel beads was determined by employing USP XXIII apparatus II (paddle method). The dissolution test was performed using 900 ml 0.1N HCL, for 2hours and at 6.8pH buffer for 10 hours, at 37 ±0.5°C at 50 rpm. Dronedarone hydrogel beads equivalent to 40 mg of Dronedarone was used for the study. At various time points (hourly) 5ml of the sample solution was withdrawn from the dissolution apparatus for upto 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at λ_{max}232nm. Dissolution profiles of the formulations were analyzed by plotting cumulative percentage drug release versus time. The data obtained were also subjected to kinetic treatment to understand release mechanism [12].

Mathematical modeling for drug release profile [13]

Zero order kinetics: It describes the system in which the drug release rate is independent of its concentration.

$Q_{ts} = Q_0 + K_0 t$

First order kinetics

It describes the drug release from the systems in which the release rate is concentration dependent.

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t/2.303$$

Higuchi model

It describes the fraction of drug release from a matrix is proportional to square root of time.

$$Mt/M\alpha = K_H t^{1/2}$$

Korsemayer-Peppas model (Power law)

The powerful law describes that the fractional amount of drug release is exponentially related to the release time and adequately describes the release of drug from slabs, cylinders and spheres.

$$Mt/M\alpha = Kt^n$$

$$\text{Log } [Mt/M\alpha] = \text{Log } K + n \log t$$

Stability Conditions

Stability study of tablets containing Dronedarone was performed at following temperatures for one month and three months [80].

1. Long term testing : 25oC/ 60%RH (1Month) (3Month)
2. Accelerated testing : 40oC/75% RH (1Month) (3Month)
   Parameters estimated: drug content

Results and discussion

Preformulation study

Solubility study: The solubility of the pure form of Dronedarone is determined to take 10mg of pure drug and observe the solubility of the drug with in different solvents, these are likes it is soluble in methanol, 0.1NHCL & $6.8P^H$ phosphate buffer, sparingly soluble in ethyl alcohol, not soluble in acetone, poorly soluble in water.

Construction of Calibration curve of Dronedarone

Determination of λ max: On the basis of preliminary identification test it was concluded that, the drug complied the preliminary identification tests. Drug was identified by UV scanning method which showed a λ at 232 nm as reported in the literature.

Preparation of standard calibration curve: From the standard curve of Dronedarone (Table 4 & Figure 10), it obeys beer's law in concentration ranges of 1 to 7µg/ml in 0.1N HCL. The linear regression equation generated was used for the calculation of amount of drug released.

Table 4: Calibration Curve data of Dronedarone

S. No.	Concentration (µg/ml)	Absorbance at λ_{max} 232nm
1.	1	0.0478
2.	2	0.1293
3.	3	0.1641
4.	4	0.2242
5.	5	0.2713
6.	6	0.3179
7.	7	0.3904

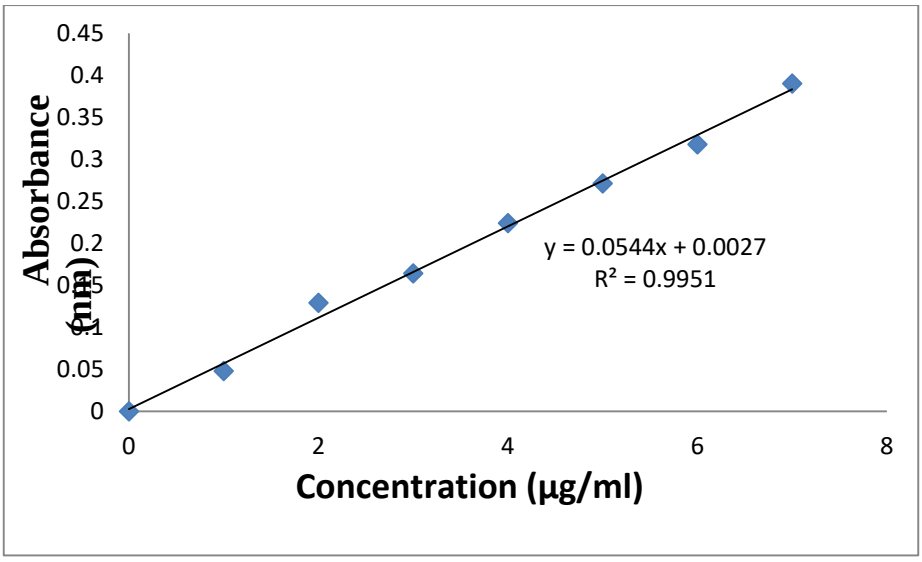

Figure 1: Calibration Graph of Dronedarone

Drug polymer interaction study

From the spectra of Dronedarone, physical mixture of Dronedarone and polymer, Dronedarone and blank beads, it was observed that all characteristic peaks of Dronedarone were present in the combination spectrum, thus indicating compatibility of the Drug and polymer. IR spectra of individual polymers and combination of Cefotaxime with all individual polymers shown in Figure 2, 3, data as shown in table 5 & 6.

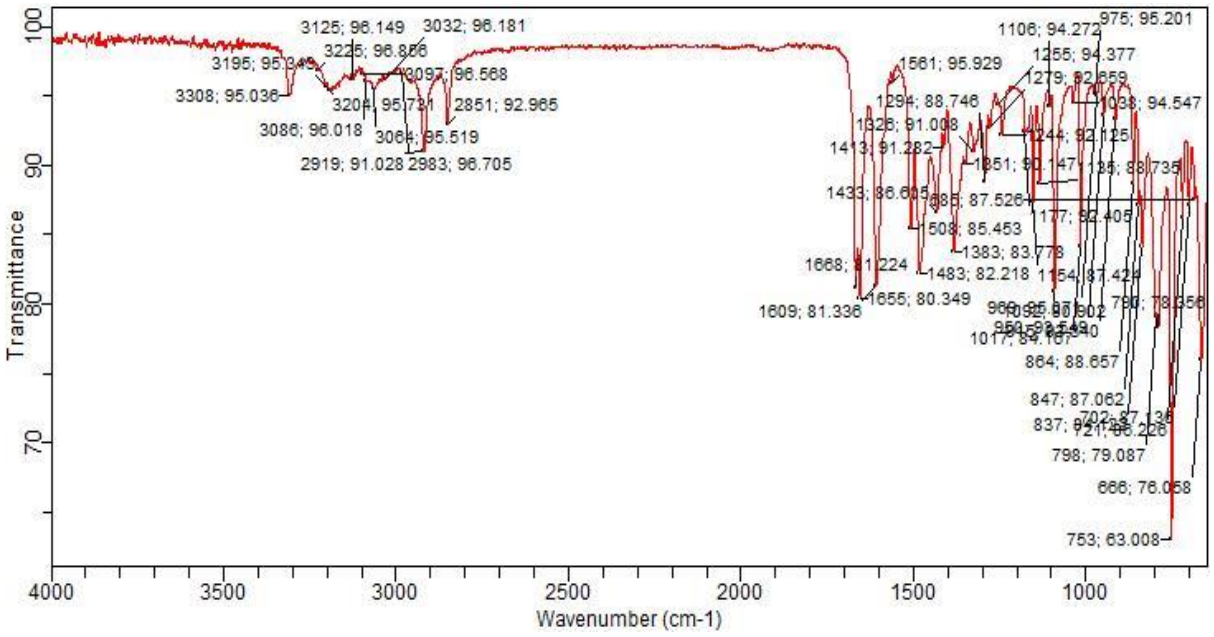

Figure 2: FTIR spectra of Dronedarone

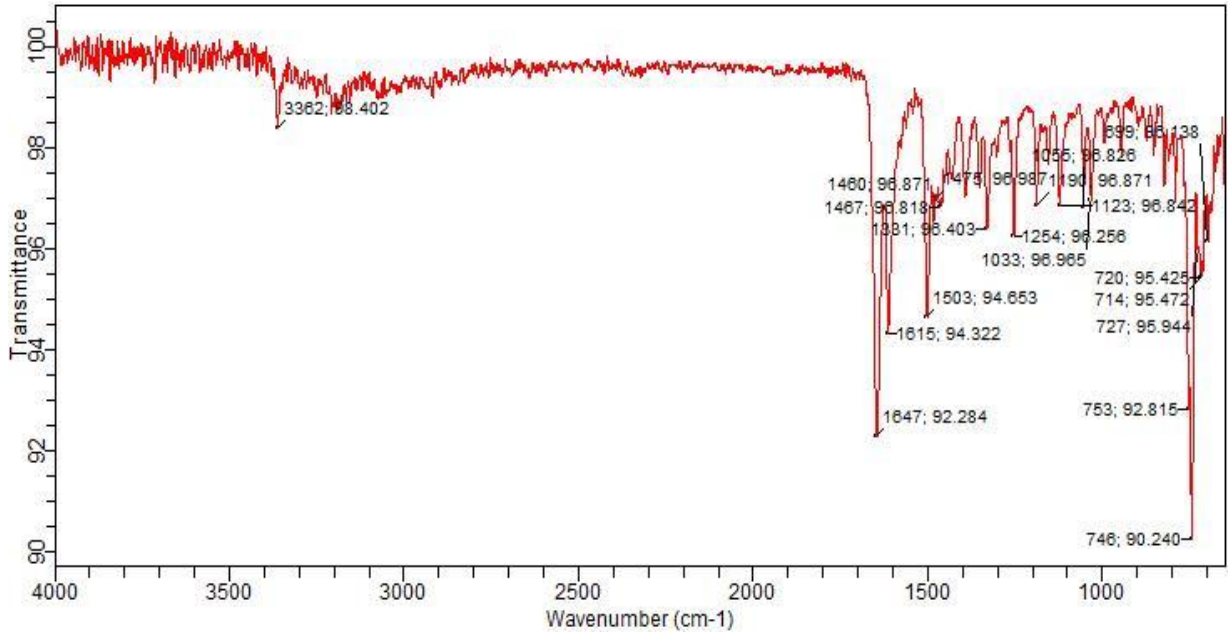

Figure 3: FTIR Spectrum of Mixtrue of compounds

Table 5: FTIR interpretation data of Dronedarone

IR Absorbance		**Bonds**	**Functional group**
Observed peak	**Characteristic peak**		
666, 685, 702, 721, 753, 790, 798, 837, 847, 864, 950, 969, 975	1000-650	(s)= C-H bend	Alkenes
	950-910	(m)O-H bend	Carboxylic acid
	900-675	(s) C-H “oop”	Aromatic
	910-665	(s, b) N-H wag	1^o,2^o amines
	850-550	(m) C-Cl stretch	Alkyl halides
	700-610	(b, s)-C# C-H:C- H bend	Alkynes
	725-720	(m) C-Br stretch	Alkyl halides
	690-515	(m) C-H rock	Alkanes
1017	1320-1000	(s)C-O stretch	Alcohol, carboxylic acid, esters, ethers
1038	1250-1020	(m)C-N stretch	Aliphatic amines
1106	1300-1150	(m)C-H Wag (-CH2X)	Alkyl halides
1244	1335-1250	(s)C-N stretch	Aromatic amines
1413,	1500-1400	(m) C-C stretch (in-ring)	Aromatics
1609	1650-1580	(m)N-H bend	1^o amines

Table 6: FTIR interpretation data of Mixtrue of compounds

IR Absorbance		**Bonds**	**Functional group**
Observed peak	**Characteristic peak**		
754, 833	1000-650	(s)= C-H bend	Alkenes
	910-665	(s, b) N-H wag	1^o,2^o amines
	900-675	(s) C-H “oop”	aromatics
	850-550	(m) C-Cl stretch	alkyl halides
1068, 1128, 1140, 1152, 1192, 1222, 1270, 1281	1320-1000	(s) C-O stretch	Alcohol, carboxylic acid, esters, ethers
	1300-1150	(m) C-H wag (-CH2X)	alkyl halides
	1250-1020	(m) C-N stretch	Aliphatic amines
	1335-1250	(s) C-N stretch	aromatic amines
1362	1370-1350	(m) C-H rock	Alkanes
1430	1500-1400	(m) C-C stretch (in-ring)	Aromatic
1464	1470-1450	(m) C-H bend	Alkanes
1595, 1626	1650-1580	(m) N-H bend	1^o amines
	1600-1585	(m) C-C stretch(in-ring)	Aromatics
1670	1760-1665	(s) C=O stretch	Carbonyls (generals)
	1710-1665	(s) C=O stretch	a , ß unsaturated aldehydes, ketones
	1680-1640	(m) –C=C- stretch	Alkenes
2996,	3300-2500	(m) O-H stretch	Carboxylic acid

3057	3000-2850	(m) C-H stretch	Alkanes
	3100-3000	(s) C-H stretch	Aromatics
	3100-3000	(m) = C-H stretch	Alkenes

Evaluation Parameters

Surface Morphology

The surface morphology of the Dronedarone beads was studied by SEM. SEM photographs of the optimized formulation. Surface smoothness was observed with guar gum incorporated Dronedarone beads [Figure 4].

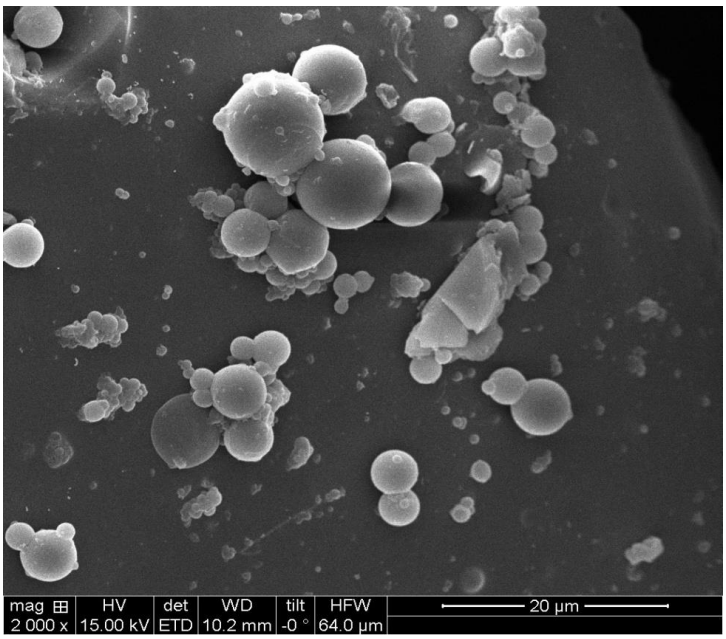

Figure 4: SEM photographs of Hydro gel beads

Frequency distribution analysis

As the ratio of polymer was increased, the mean particle size of Dronedarone beads had also decreased (Table 7). The significant decrease may be due to the increase in the viscosity of the droplets. Dronedarone beads having a size range of 1. to 1. mm with normal frequency distribution was obtained.

Percentage yield

Percentage practical yield of Dronedarone hydrogel beads was calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Dronedarone beads recovered from each batch in relation to the sum of starting material were given in table 7.

Drug Content

The Drug Content increased with increase in the polymer concentration. From the results it can be inferred that there is a proper distribution of Dronedarone in the beads and the deviation were within the acceptable limits as shown in the table 7.

Percentage drug entrapment efficiency

Entrapment efficiency increased with increase in the polymer concentration. From the results it can be inferred that there is a proper distribution of Dronedarone in the beads and the deviation were within the acceptable limits. By increasing the polymer concentration, the encapsulation efficiency was increased [Table 7]. The entrapment efficiency of high in beads that were formulated by using carbopol.

Table 7: Average particle size of Dronedarone Hydrogel beads.

Formulation code	Average size (mm)	Percentage Yield	Entrapment efficiency (%)	Drug Content (%)
F1	1.1	83.31	73.24	75.43
F2	1.3	86.17	67.13	65.33
F3	1.4	88.38	81.79	79.37
F4	1.1	83.20	77.84	82.35
F5	1.2	85.15	82.84	89.42
F6	1.4	89.35	85.62	87.68
F7	1.2	88.50	77.53	90.33
F8	1.4	91.55	84.22	95.77
F9	1.1	92.63	83.24	94.35
F10	1.2	93.38	77.15	96.69
F11	1.2	94.33	89.17	97.76
F12	1.2	95.42	97.18	98.83

***In vitro* dissolution studies**

The in vitro performance of Dronedarone hydrogel beads showed prolonged and controlled release of Dronedarone. The results of the in vitro dissolution studies showed controlled release in a predictable manner. As the polymer concentration was increased, the drug release from the hydrogel beads was found to decrease. Compared to sodium CMC and HPMC K4M, Carbopol retarded drug release more effectively, hydrogel beads had an optimum release at the end of 12th hour. The in vitro release profiles of all the formulations (F1 to F12) are shown in tables 8 and Figure 5.

Table 8: In vitro release data of sodium alginate Hydrogel beads of Dronedarone.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	31.44	25.27	18.35	21.33	13.50	14.44	25.34	27.44	9.17	21.61	9.53	8.53
1	48.64	43.18	27.42	37.44	21.51	28.82	38.31	35.31	21.31	35.17	13.17	12.47
2	61.22	55.82	38.92	44.85	35.82	32.50	45.31	42.31	34.42	47.33	27.35	36.48
3	75.16	64.32	41.43	53.72	48.73	45.32	51.84	55.74	46.50	57.27	38.45	48.53
4	87.32	78.65	53.86	67.87	57.35	53.64	62.52	64.33	53.57	65.57	45.37	55.62
5	-	86.23	62.62	74.33	68.82	63.87	71.63	73.33	64.31	72.30	54.31	64.40
6	-	92.24	73.55	88.86	75.32	82.33	87.91	88.31	74.31	83.32	66.33	76.41
8	-	-	86.22	91.42	81.34	94.55	-	90.43	84.44	88.31	78.25	88.27
10	-	-	91.31	-	93.51	-	-	-	-	96.31	87.28	91.21
12	-	-	-	-	-	-	-	-	-	-	96.17	98.32

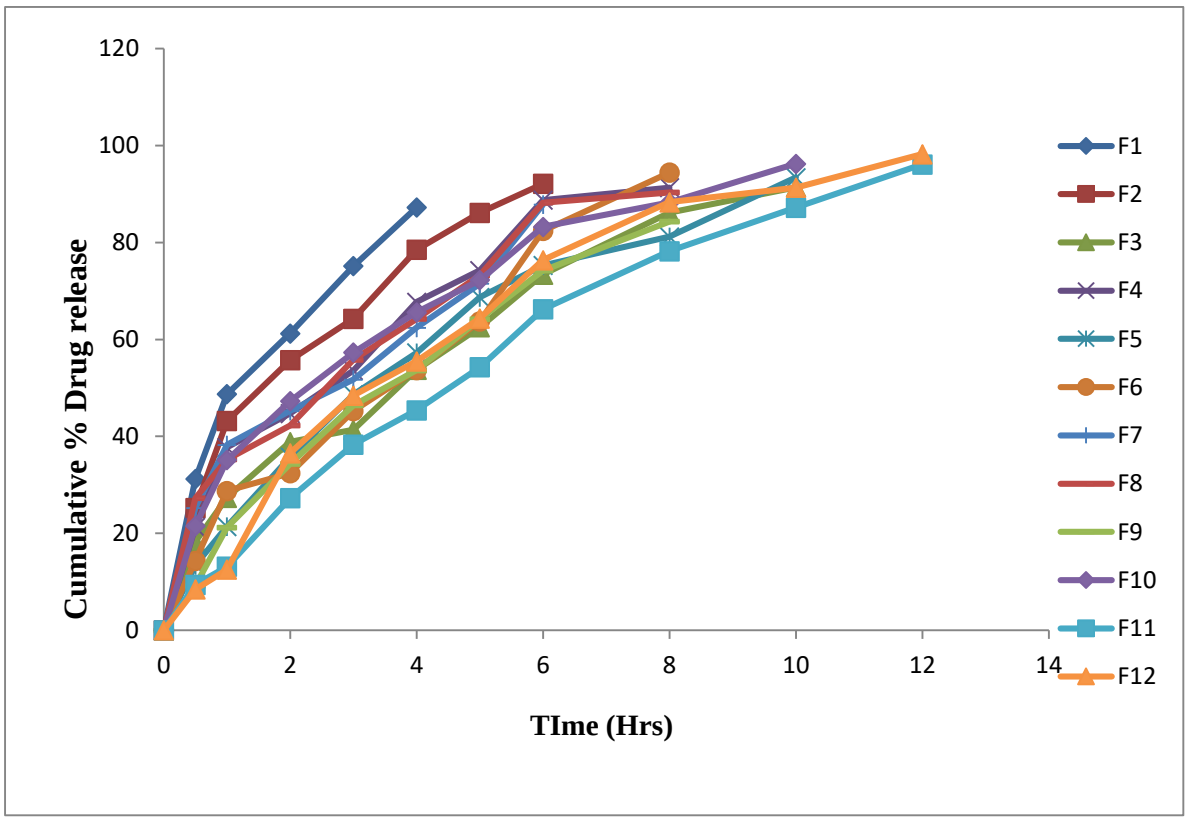

Figure 5: *In vitro* release data of sodium alginate Hydrogel beads of Dronedarone

Release Order Kinetics of Dronedarone Hydrogel Beads

The invitro dissolution data for best formulation F9 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. As its value nearer to the '1' it is conformed as it follows the zero order release [Table 13]. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot [Figure 6, 7, 8 and 9].

Table 9: Release order kinetics of zero order kinetics

S.No	Time	% cumulative drug release
1	0	0
2	5	15754
3	10	29079
4	15	36888
5	20	35645
6	25	42389
7	30	50240
8	35	56233
9	40	65870
10	45	91930
11	50	92333
12	55	93456

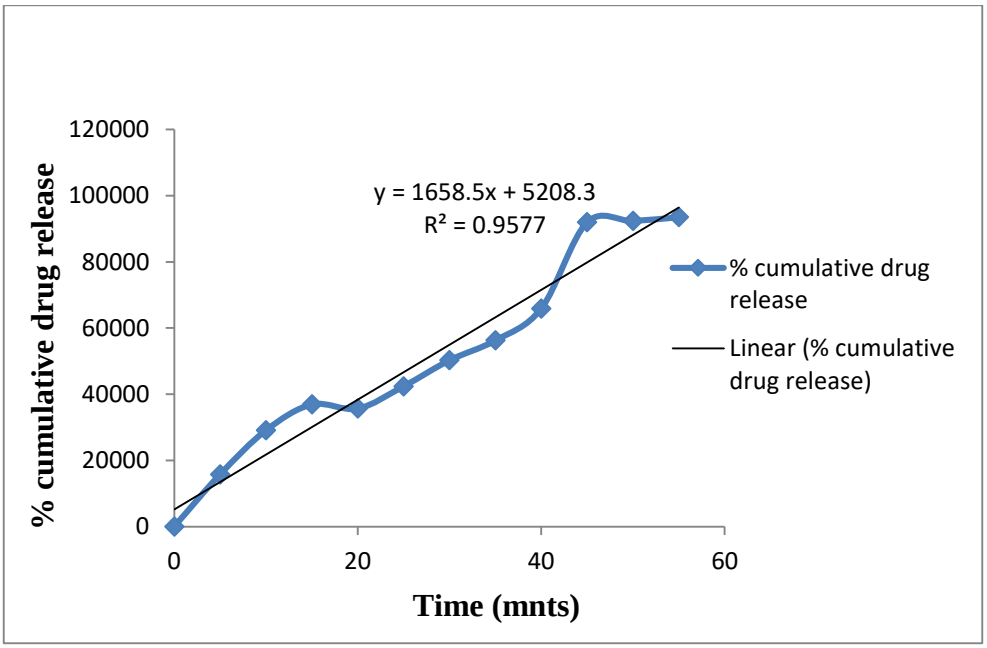

Figure 6: F12of *In vitro* dissolution studies of zero order kinetics

Table 10: Release order kinetics of first order kinetics

S.No	Time	Log cumulative % drug release
1	0	0
2	5	4.195
3	10	4.535
4	15	4.656
5	20	4.602
6	25	4.706
7	30	4.788
8	35	4.787
9	40	4.890
10	45	4.856
11	50	4.922
12	55	4.967

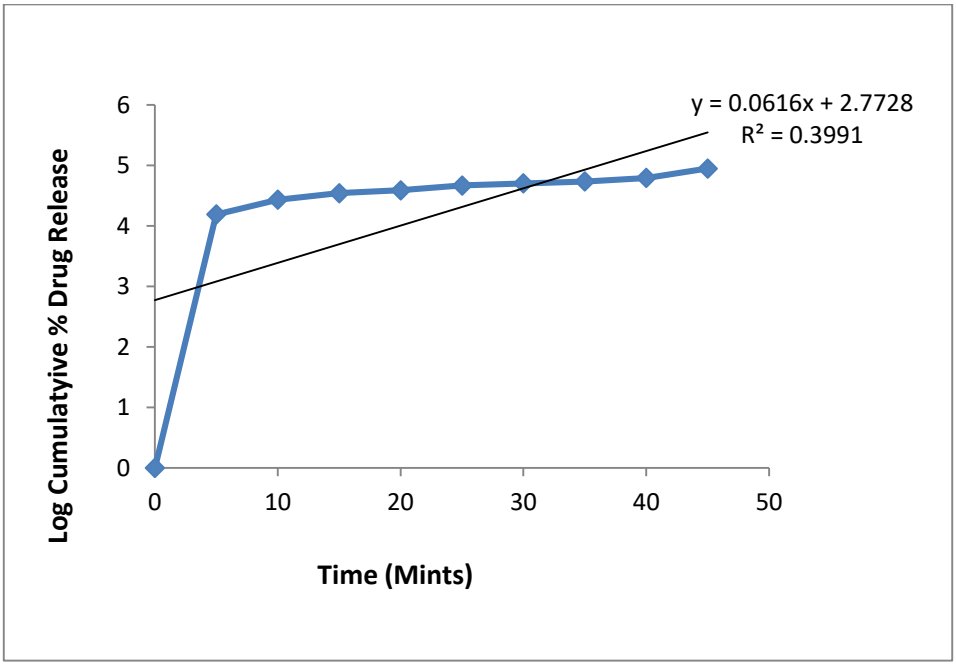

Figure 7: F12 of *In vitro* dissolution studies of first order kinetics

Table 11: Release order kinetics of korsmeyer peppas

S.No	Time	Log cumulative % drug release
1	0	0
2	5	4.443
3	10	4.266
4	15	4.454
5	20	4.720
6	25	4.477
7	30	4.750
8	35	4.644
9	40	4.809
10	45	4.936
11	50	4.989
12	55	4.999

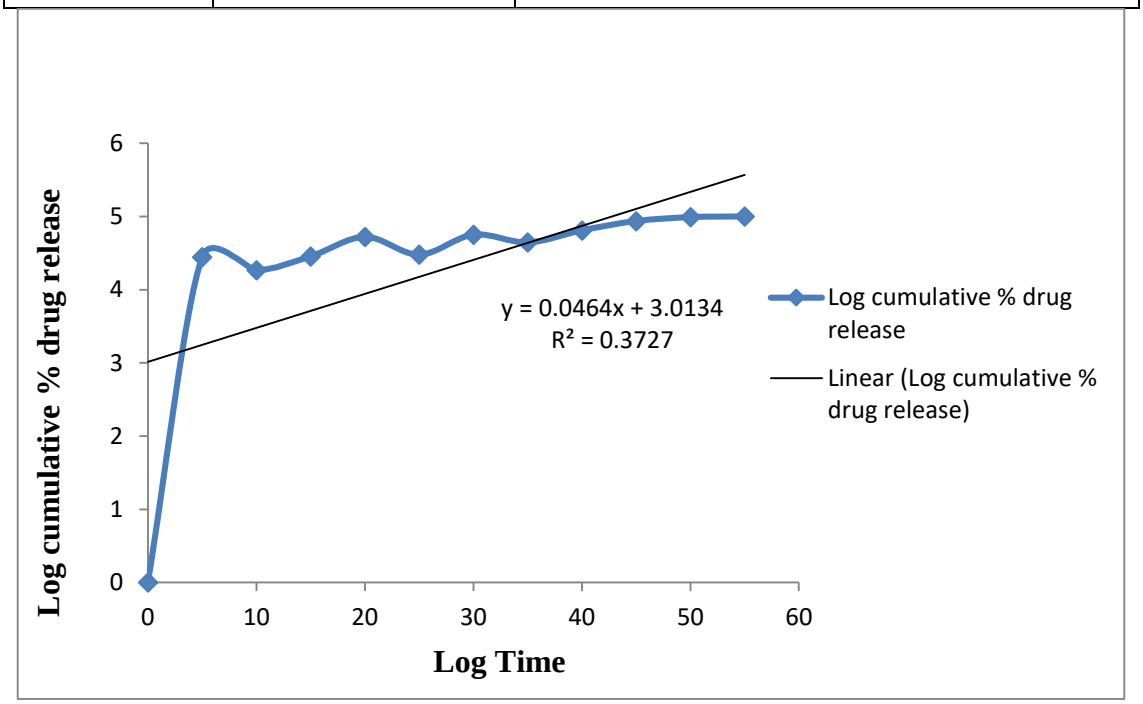

Figure 8: F12of *In vitro* dissolution studies of korsmeyerpeppas

Table 12: Release order kinetics of Higuchi

S.No	Square root of time	% cumulative drug release
1	0	0
2	2.24	15670
3	3.17	27115
4	3.88	34657
5	4.48	39733
6	5	47350
7	5.48	52334
8	5.92	55022
9	6.33	60345
10	6.75	87886
11	7.08	89666
12	7.20	91235

Figure 9: F12 of *In vitro* dissolution studies of Higuchi

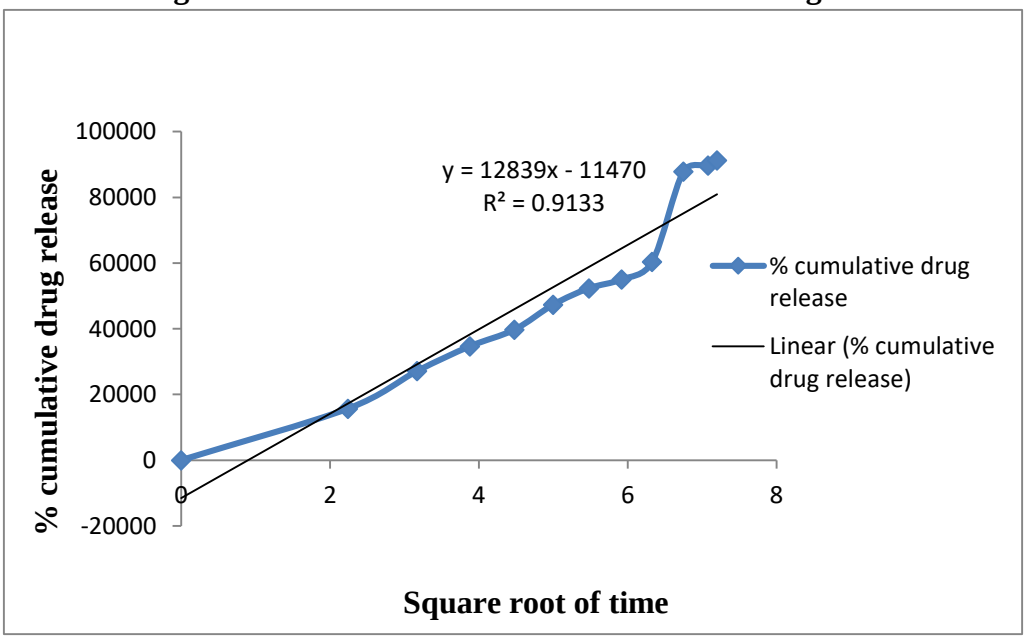

Table 13: Drug Release Kinetics

Batch	**Zero Order**	**First Order**	**Higuchi**	**Peppas**	**Peppas**
Code	**r^2**	**r^2**	**r^2**	**r^2**	n
F1	0.966	0.822	0.948	0.623	1.032
F2	0.978	0.816	0.949	0.632	1.022
F3	0.976	0.822	0.966	0.612	1.023
F4	0.962	0.843	0.964	0.633	1.032
F5	0.951	0.811	0.987	0.621	1.018
F6	0.962	0.843	0.945	0.624	1.013
F7	0.964	0.832	0.963	0.618	1.017
F8	0.977	0.811	0.977	0.617	1.018
F9	0.967	0.388	0.888	0.776	1.012
F10	0.979	0.812	0.945	0.637	1.021
F11	0.973	0.824	0.963	0.615	1.022
F12	0.957	0.356	0.372	0.913	1.024

Stability study: Optimized formulation F12 was subjected to stability studies for 1 to 3 months and the tablets were tested for drug content. The results obtained were as in the following table 14.

Table 14: Stability studies of the optimized formulation F12

Time in hrs	Drug Content		
	F12	After 1 Month	After 3 Month
1	75.43	75.41	74.31
2	65.43	65.31	64.31
3	79.22	79.14	80.38
4	82.24	82.43	81.61
5	89.41	89.45	90.43
6	87.28	87.14	86.46
7	90.27	90.32	91.65
8	95.67	94.34	94.61
9	94.34	93.25	93.54
10	96.49	95.88	95.68
11	97.32	96.77	96.32
12	98.57	97.57	96.68

Conclusion

Preformulation studies like solubility and UV analysis complied with standards. The FTIR Spectra revealed that, there was no interaction between Dronedarone and polymers. Surface smoothness of the Dronedarone beads was confirmed by SEM.As the ratio of polymer was increased, the mean particle size of Dronedarone hydrogel beads was decreased. Dronedarone hydrogel beads with normal frequency distribution were obtained. Entrapment efficiency increased with increase in the polymer concentration. From the results it can be inferred that there was a proper distribution of Dronedarone in the beads and the deviation was within the acceptable limits. The study also indicated that the amount of drug release decreases with an increase in the polymer concentration. The *in vitro* performance of Dronedarone Hydrogel beads showed prolonged and controlled release of drug. The *in vitro* dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F12 shows r^2 value 0.957. As its value nearer to the '1' it is conformed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot. The 'n' value is 1.021 for the optimized formulation (F12) i.e., n value was >0.89 this indicates Super case transport.

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