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STUDY THE POLYMER ABSORPTION ON PHYSICAL EFFECT AND DRUG RELEASE OF DICLOFENAC SODIUM MICROSHPERES.

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ABSTRACT

Diclofenac sodium is a potent non-steroidal drug with potent analgesic and anti-inflammatory activity. Its oral administration is associated with a high risk of adverse effect such as irritation, ulceration and bleeding of gastrointestinal tract. The present study focuses on the development of controlled release drug delivery system of diclofenac sodium. Diclofenac Sodium microspheres were prepared successfully using the solvent evaporation method. Polymer: drug ratio influenced the physicochemical properties microspheres. From the experimental results it can be concluded that biocompatible and cost-effective polymers like ethyl cellulose can be used to formulate an efficient microparticulate system with good percentage entrapment efficiency and practical yield. The ratio of polymer in dispersion medium was the controlling factors of microsphere micrometric parameters and drug release. Higher percentage of drug loading was obtained by increasing the concentration of polymer. The microspheres showed good flow properties and packing ability, indicating that it can be successfully handled and filled into a capsule dosage form. The particle size of a microsphere was determined by optical microscopy and all the batches of microspheres show uniform size distribution. It was observed that with increase in polymer concentration, the mean particle size of the microspheres increased. The *in-vitro* dissolution studies showed that Diclofenac Sodium microspheres formulation F4 showed better sustained effect (94%) over a period of 8 hours than other formulations.

KEYWORDS: Microsphere, diclofenac sodium, calcium chloride, solvent evaporation method, ethyl cellulose.

INTRODUCTION

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm (1 mm). Microspheres are sometimes referred to as spherical micro particles. In general microspheres are solid or hollow and do not have a fluid inside, as opposed to microcapsules.

Glass microspheres, polymer microspheres, metal microspheres and ceramic microspheres are generally available.

Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are normally used as additives to lower the density of a material. Solid microspheres have various applications depending on what material they are manufactured of and what size they are.

Microspheres made from highly transparent glass can perform as very high quality optical micro cavities or optical micro resonators.

Ceramic microspheres are used primarily as crushing media.

Hollow microspheres loaded with drug in their outer polymer shell were prepared by a novel emulsion solvent diffusion method and spray drying technique.

Microspheres vary widely in quality, sphere, uniformity and particle size distribution. The proper microsphere needs to be chosen for each different application.

Diclofenac sodium is a potent non-steroidal anti-inflammatory with analgesic and antipyretic properties. It is used for the long term therapy of chronic musculoskeletal pain, chronic swelling condition and for treatment of rheumatoid arthritis. Diclofenac sodium has a short life not more than two hrs. Which require multiple dosing for maintaining therapeutic effects throughout the day.

Solvent evaporation method is simple dispersing a drug in a solid dispersion. It requires only mild condition of temperature and continuous stirring.

AIM AND SCOPE OF WORK

Controlled drug delivery system received tremendous attention and the significant research interest in the long term maintenance of drug levels coincides with the increased medical and public acceptance of such systems. Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, least sterility constraints and flexibility in the design of the dosage forms. The primary objective of zero-order release is to up-hold constant drug concentration in blood for a prolonged period of time.

Microspheres have potential to deliver drug in a controlled released fashion. In case of microspheres as a drug delivery system, various biodegradable polymers and manufacturing methods are available. The applications of microencapsulation might well include sustained-release or prolonged action medication.

Administration of drugs in the form of microspheres, usually improves the treatment by providing the localization of the active substance at the site of action and by prolonging release of drug.

Diclofenac Sodium is an effective antihypertensive and diuretic drug but the dosage form of drug have very short half-life only 1-2 hrs. Due to this it quickly eliminated from blood circulation. Thus, development of controlled release dosage forms would clearly be advantageous.

Plan of work

Physiochemical studies

Microspheres of Diclofenac sodium were prepared by solvent evaporation method using Ethyl cellulose and calcium chloride. Weighed quantity of drug and polymer were added to 50 ml of Ethyl cellulose solution with stirring at about 300 rpm. The resultant solution was then added drop wise to 100 ml of calcium chloride solution under continuous stirring. Stirring was continued for 30 minutes. The obtained microspheres were filtered and washed with purified water and then dried for 6 hours at 40°C. Preparation of microspheres was optimized based on entrapment efficiency and release data.

The dried microspheres were sifted through mesh 30 ASTM. Tablets were compressed so that each tablet contained microspheres equivalent to 100 mg of drug. Hardness was maintained at 4-5 KP and tested for friability. The tablets were found to meet the friability limit of 0.1% w/w.

MATERIALS AND METHODS

Materials

Diclofenac sodium, ethyl cellulose, calcium chloride.

Dissolution studies

Dissolution studies of different formulations were carried out in the following conditions,
Apparatus: USP II.
Media: Acid stage: 0.1 N Hydrochloric acid for 2 hours Buffer stage: 0.05 M pH 7.5 Phosphate buffer for 12 hours RPM: 75 Time points: 1, 2, 4, 6, 10 and 12 hours in buffer stage. UV Wavelength: 276 nm.

Details of composition of various formulations prepared are mentioned in the below table.

Drug entrapment efficiency

Encapsulation efficiency = (actual drug loading / theoretical drug loading) X 100%.

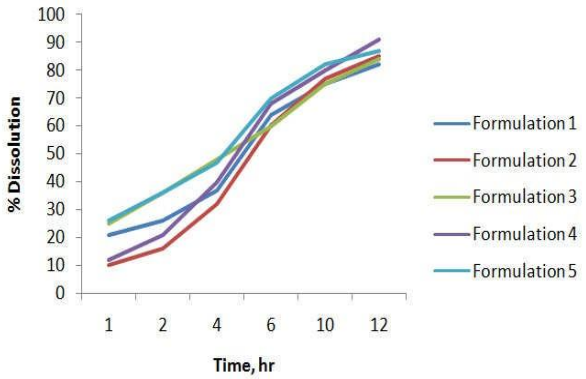

Fig. 1: It shows *In vitro* Dissolution profile of the prepared formulations.

Drug loading depends on the solubility of the drug in the external phase. Stirring time becomes very critical for water soluble drugs as they may diffuse into the gelatin medium leading to decreased efficiency of encapsulation of the drug.

Table 1: It shows the composition of the prepared formulations.

Drug: Diclofenac sodium	Ethyl cellulose solution (% w/v)	Calcium chloride Solution	Formulation code
F1	1:1	4	5
F2	1:2	4	5
F3	**2:1**	2	5
F4	**1:2**	2	5

Flow property

Flow of microspheres was studied by assessing angle of repose. Prepared microspheres were allowed to fall freely through a funnel fixed at 1 cm above a flat surface until the microspheres touched the tip of the funnel.
$\theta = Tan^{-1} (H/R)$

H - Height of cone
R - Radius of microspheres on surface.

DISSOLUTION

An aliquot of sample was withdrawn at suitable time intervals and the same amount of volume was replaced with fresh dissolution medium.

Kinetics: To understand the kinetics of drug release, dissolution data of the formulations was fitted to various release models.

RESULTS AND DISCUSSION

Particle size decrease by increasing the mixing speed of calcium chloride solution and increase by increase in the ethyl cellulose concentration.

With increase in the concentration of ethyl cellulose, drug entrapment efficiency and particle size were found to increase.

The percentage entrapment efficiency was found to be between 40 and 85 depending upon the process parameters. The microsphere obtained by longer exposure to the cross linking agent have shown lower entrapment efficiency but sustained the release of diclofenac sodium.

Angle of repose obtained for different formulations was between 29 and 37°.

Release of diclofenac sodium from the tablet was studies for a period of 12 hours in phosphate buffer after 2 hours exposure in acid media.

Table 2: It shows % drug release data observed for various formulations in buffer stage.

Time, hrs.	Formulation 1	Formulation 2	Formulation 3	Formulation 4
1	21±1.23	10±1.21	25±1.32	12±1.13
2	26±1.34	16±1.22	36±1.16	21±1.21
4	37±1.11	32±1.23	48±1.19	40±1.24
6	64±1.12	60±1.27	60±1.34	68±1.18
10	75±1.32	77±1.13	75±1.27	80±1.26
12	82±1.26	85±1.21	84±1.24	91±1.25

The release was observed to be slow and extended. Due to low solubility of ethyl cellulose and diclofenac sodium being practically insoluble in acidic medium, there was no observable release of diclofenac sodium in 0.1 N HCL. Among the formulations, suitable sustained release till 12 hours was obtained with formulation F4.

Drug release data of F4 was best fitted to Michaelis Menten model. The clinical implication of Michaelis-Menten pharmacokinetics is that the clearance is not constant as it is with linear pharmacokinetics, but is concentration or dose-dependent.

Table 3: It shows the drug release kinetics of different formulations

Model	Parameters	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Zero order	RMSE	5.63±0.02	5.74±0.03	3.12±0.03	6.98±0.04
	AIC	3.55±0.03	3.57±0.05	2.84±0.01	3.81±0.04
	BIC	3.51±.0.03	3.53±0.04	2.80±0.05	3.76±0.06
	R^2	9.44±0.05	9.61±.0.04	9.77±.0.04	9.44±.0.05
First order	RMSE	9.62±0.03	1.50±0.04	6.24±0.02	1.56±0.04
	AIC	4.19±0.08	4.73±0.07	3.67±0.02	4.77±0.02
	BIC	4.15±0.08	4.68±0.07	3.63±0.05	4.73±0.07
	R^2	8.98±0.04	8.67±0.03	9.01±0.05	8.36±0.06
Korsemeyer Peppa's	RMSE	4.72±0.05	5.47±0.02	8.29±0.01	6.49±0.03
	AIC	3.34±0.02	3.51±0.03	1.25±0.02	3.72±0.02
	BIC	3.29±0.04	3.47±0.02	1.21±0.03	3.68±0.03
	R^2	9.59±0.02	9.83±0.03	9.99±0.02	9.83±0.01
Hixson Crowell	RMSE	7.88±0.03	1.05±0.02	1.50±0.03	1.15±0.02
	AIC	3.95±0.02	4.29±0.04	3.41±0.02	4.41±0.01
	BIC	3.91±0.03	4.25±0.03	3.36±0.01	4.37±0.02
	R^2	9.17±0.01	9.09±0.02	9.33±0.02	8.82±0.03
Michaelis Menten	RMSE	1.01±0.03	6.55±0.03	5.74±0.02	4.70±0.02
	AIC	4.25±0.04	3.73±0.02	3.56±0.01	3.33±0.03
	BIC	4.21±0.02	3.69±0.03	3.52±0.03	3.29±0.02
	R^2	8.97±0.01	9.82±0.02	9.78±0.02	9.95±0.03

CONCLUSION

Sustained release formulation of Diclofenac Sodium was successfully prepared using Ethyl cellulose by solvent evaporation method. The in vitro dissolution data showed sustained release of the formulation up to 12 hours. The microspheres were prepared without the use of organic solvents. Microspheres of Diclofenac sodium decrease the incidence of side effects and also improve patient compliance by reducing the number of dosing and by reducing the fluctuations of drug in the blood.

Four batches with different drug is to polymer ratios (Diclofenac Sodium: ethyl cellulose: 1:1, 1:2, 1:3, & 1:4) were prepared and evaluated using various analytical techniques like micrometric properties, particle size, percent drug encapsulation efficiency and in vitro dissolution studies.

(1) Percentage yield

The percentage yield of four formulations was ranging from 83.86±1.23% to 96.99±1.31% respectively (Table 4). This higher percentage yields indicates that this method was very useful for adoption in the formulation of Diclofenac Sodium microsphere. The maximum yield was obtained with formulation F4. It indicates that percentage yield is increases when the concentration of polymer increases.

Table 4: Data for % yield of Diclofenac Sodium microspheres.

Formula Code	% yield
F1	83.86±1.23
F2	87.65±1.47
F3	94.56±1.34
F4	96.99±1.31

(2)Bulk Density and Tapped Density

Study of bulk density and tapped density are important as density of microspheres defines its packaging. Tapped density gives information on consolidation of microspheres. Consolidated microspheres likely to have a greater arch strength than a less consolidated one, and may therefore be more resistant to powder flow. The bulk density of four formulations was ranging from 0.46±0.03 to 0.57±0.08. The tapped density of four formulations was ranging from 0.52±0.04 to 0.64±0.02. Formulation F4 shows lowest bulk density and lowest tapped density. The lower values of densities indicate that F4 formulation is more bulky. Tapped density and bulk density are shown in table 5 with different formulation.

Table 5: Data for bulk and tapped density.

Parameters	Formulations			
	F1	F2	F3	F4
Bulk Density(g/ml)	0.46±0.03	0.57±0.08	0.49±0.06	0.44±0.03
Tapped Density (g/ml)	0.52±0.07	0.64±0.02	0.55±0.05	0.50±0.04

3) Carr's Index and Hausner's Ratio

Carr's index and Hausner's ratio has been used as an indirect method of quantifying powder flow ability from bulk density and tapped density. The smaller the Carr's Index and Hausner's ratio the flow property is higher. The value of Carr's index of four formulations was ranging from 10.90±0.41 to 12±0.33 and value of Hausner's ratio was ranging from 1.12±0.43 to 1.13±0.23. All microspheres showed good flow characteristics according to USP 28-NF 23 criteria, with Hausner's ratio less than 1.18 and percentage of compressibility less than 15. In consideration of compressibility index and Hausner's ratio, F3 microspheres were appeared predominant in flowability. Carr's index and Hausner's ratio of different formulations are shown in table 6.

Table 6: Data of Carr's index and Hausner's ratio.

Parameters	Formulations			
	F1	F2	F3	F4
Carr's index	11.53±0.43	10.93±0.21	10.90±0.41	12±0.33
Hausner ratio	1.13±0.23	1.12±0.32	1.12±0.43	1.13±0.19

(4) Angle of repose

Angle of repose is a characteristic related to inter-particulate friction or resistance to movement between particles. Angle of repose of four formulations was ranging from 23° 48' to 26° 51'. Angle of repose values of all microspheres did not exceed 27º and the microspheres were accepted as free-flowing. Regarding the flow rates, F3 microspheres flowed faster, confirming its powder properties.

Table 7: Data of Angle of repose of microspheres.

Parameters	Formulation code			
	F1	**F2**	**F3**	**F4**
Angle of repose	**24° 37'**	**25° 24'**	**23° 48'**	**26° 51'**

(5)Particle size analysis

The microspheres were viewed under the optical microscope to study their properties and to perform the particle size analysis. In all the batches of formulations (F1-F4) the microspheres were found to be spherical and discrete. Mean particle size was determined by optical microscopy and the average particle size were calculated for each formulation The average particle size of the formulations F1, F2, F3 and F4 were 224.64 µm, 349.16 µm, 357.43 µm , 361.71 µm respectively . Increase of average particle size with increase in polymer concentration was observed, which may be due to the fact that the increase in polymer concentration leads to a significant increase in the viscosity in a fixed volume of solvent, thus leading to an increase of the emulsion droplet size and finally a higher microsphere size. (table 8).

Table 8: Data of particle size.

Formulation	Average particle size(µm)
F1	224.64±01
F2	349.16±01
F3	357.43±01
F4	361.71±01

(6) Drug loading efficiency/ content uniformity

The test for content uniformity was carried out to ascertain whether the drug is uniformly distributed in the formulation. The results obtained are reported in Table 6. From the results it can be inferred that there is proper distribution of Diclofenac Sodium in the microspheres and the deviation is within acceptable limits. From the three formulations F4 has the highest percentage of the drug content following by other formulations. Because it may be due to the highest amount of theoretical drug content and highest percentage yield in this ratio.

Table 9: Data of drug loading efficiency.

Formulation	% drug Content
F1	65.4±0.1
F2	68.7±0.3
F3	70.5±0.2
F4	74.3±0.2

(7): *In vitro* dissolution studies of microspheres

Microspheres of all batches had faster initial drug release approximately 25 percentages within 15 minutes. Then the release was slow and sustained over 8 hours, depending upon the polymer: drug ratio. By the end of 8th hour the percentage of drug release was found to 79.22, 84.72, 88.97 and 94.12 for F1, F2, F3 and F4 formulation respectively. The formulation F4 showed better sustained release (94%) at the end of the 8th hour as compared to other batches. This may be due to better loading, encapsulation efficiency and increased particle size as compared to other batches.

Table 10: Dissolution Profile of F1-F4 formulations (1:1, 1:2, 1:3, and 1:4 of ethyl cellulose)

Time	F1	F2	F3	F4
1	28.32±0.02	29.12±0.02	31.56±0.03	33.32±0.02
2	36.73±0.03	40.22±0.04	44.67±0.02	49.98±0.03
3	40.06±0.04	43.28±0.03	55.91±0.03	59.24±0.02
4	47.65±0.03	51.06±0.02	66.28±0.03	71.56±0.02
5	55.65±0.02	58.87±0.03	75.08±0.02	75.67±0.03
6	61.24±0.03	66.88±0.02	79.96±0.01	77.68±0.03
7	74.64±0.02	73.96±0.03	83.76±0.02	85.21±0.03
8	79.22±0.01	84.72±0.02	88.97±0.03	94.12±0.03

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