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Sustained Release Agglomerates of Ibuprofen Using Natural Polymer and Thermal Gelation Technique

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Ibuprofen-carrageenan agglomerates were prepared by the method of thermal gelation in the liquid media. Agglomerates having a mean diameter in the range of 1000-1300 μ and entrapment efficiency of 60-80% were obtained. Scanning electron micrographs of drug-loaded microspheres showed that agglomerates are spherical in shape and had a rough surface texture. Fourier transform infrared spectroscopy and differential scanning calorimetric analysis confirmed the absence of any drug-polymer interaction. X-ray diffraction patterns showed that ibuprofen in the agglomerates was unchanged in crystalline form. The micromeritic properties of agglomerates found to be slightly changed by changing various processing parameters to give agglomerates of good flow property. The *in vitro* release profile could be altered significantly by changing various processing parameters to give a sustained release of drug from the agglomerates.

The non-steroidal antiinflammatory drug, ibuprofen is good candidate for the development of oral controlled release formulation. Adverse gastrointestinal reactions have been observed and short biological half-life requires a three times a day administration[1]. Orally administered drugs which are promptly absorbed in the alimentary canal and rapidly lost from the blood are generally single unit film coated solid dosage forms[2]. However, such unit solid dosage forms could be disastrous if they fail to release the drug at the desired rate and in the desired amount, or release the entire amount of drug so as to cause dose dumping. Microencapsulation has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal irritation[3,4]. In addition, multiparticulate delivery systems can be distributed widely throughout the gastrointestinal tract providing a possibility of achieving a longer lasting and more reliable release of drugs. Unwanted intestinal retention of the polymeric material and local irritation, which may occur with nondisintegrating polymeric matrix tablets, can also be avoided[5].

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These considerations led to the objective of this study to prepare and evaluate oral multiparticulate delivery system of the ibuprofen using carrageenan. Carrageenan is a natural water-soluble hydrocolloid, made up of repeating galactose units containing 3,6-anhydro-D-galactose both sulphate and non-sulphate, linked by alternate α-1,3 and β-1,4-glycosidic linkages. Carrageenan has been extensively tried as thickening and gelling agent in the food and cosmetic industries[6]. Spherical agglomerates of water insoluble drug using carrageenan have been tried in the endeavor to control the drug release from spheres prepared by cross-linking technique[7].

In the present study, agglomerates of ibuprofen prepared by thermal gelation method using carrageenan polymer were characterized. The effect of drug and polymer concentration on the physical properties and on the drug release was evaluated. Various process parameters like drug polymer ratio, stirring speed, stirring time and volume of oil were optimized. These spherical agglomerates were evaluated for drug content, particle size distribution and other micromeritic properties and *in vitro* drug release. Drug-polymer interactions in the solid state were studied by

TABLE 1: EFFECT OF VARIOUS PROCESSING AND FORMULATION PARAMETERS ON THE ENTRAPMENT EFFICIENCY OF DRUG- LOADED AGGLOMERATES

Processing and formulation parameters		Theoretical content (%)	Actual content (%)	Entrapment efficiency* (%) *SD <2.0
Drug-polymer ratio	1:1	50.00	32.15	64.30
	2:1	66.67	44.29	66.37
	3:1	75.00	58.32	77.77
	4:1	80.00	65.10	81.37
Volume of vegetable oil (ml)	300	80.00	65.22	81.53
	400	80.00	67.19	83.99
	500	80.00	69.54	86.93
Stirring speed (rpm)	75	80.00	54.79	68.49
	100	80.00	63.80	79.75
	150	80.00	65.90	82.37
Stirring time (h)	2	80.00	65.09	81.37
	4	80.00	56.54	70.68
	6	80.00	60.00	75.01
	8	80.00	58.00	72.51

infrared spectrophotometry, differential scanning calorimetry, X-ray diffraction studies and scanning electron microscopy.

MATERIALS AND METHODS

Ibuprofen was a gift sample from Sekhsaria chemicals Ltd., Mumbai. Carrageenan (Type: Gelcarin GP 812) was provided by FMC Biopolymers, USA. Sunflower oil (food grade) was a gift sample from Godrej oil limited, Mumbai. All reagents and solvents used were of analytical grade.

Preparation of agglomerates:

The aqueous dispersion of carrageenan (1 g) was prepared in 80 ml of distilled water and heated to 60-65°. The drug (1-4 g, previously passed through 200#) was added to the carrageenan dispersion with stirring and the dispersion was diluted to a volume of 500 ml with distilled water. The dispersion was kept at 60-65°. The drug-loaded agglomerates were formed by dropping the drug-polymer dispersion by a jacketed glass syringe (provided with hot water (60-65°) supply), into previously cooled sunflower oil (10°, maintained by ice-salt freezing mixture) with constant stirring. The stirring was continued for 2-8 h for the hardening of agglomerates. The resulting agglomerates were decanted, freed of sunflower oil by continuously washing with isopropyl alcohol and finally air dried for 24 h. The dried microspheres were stored in a dessicator at ambient temperature until further evaluation.

Drug loading assay:

About 50 mg of accurately weighed drug loaded agglomerates were added to 100 ml of pH 7.2 phosphate buffer. The resulting mixture was kept for shaking on mechanical shaker for 24 h. The solution was filtered (0.45μ pore size) and 1 ml of this solution was appropriately diluted using pH 7.2 phosphate buffer and analyzed spectrophotometrically at 264 nm using Milton Roy UV/Vis Spectrophotometer. The solution obtained after similar treatment of blank agglomerates was used as blank for assay of drug to counteract any possible interference due to carrageenan.

Size distribution of agglomerates:

Size distribution of the agglomerates was determined using standard test sieves. Particles which passed through

TABLE 2: MICROMERITIC PROPERTIES OF DRUG-LOADED AGGLOMERATES

Processing and formulation parameters		Angle of repose[a] (°) [a]SD<2.0	Bulk density[b] (g/ml) [b]SD<0.05	Tap density[b] (g/ml) [b]SD<0.05	Mean particle size[c] (μm) [c]SD<1.0
Original drug crystals		43.71	0.384	0.575	–
Drug-polymer ratio	1:1	32.15	0.452	0.465	810
	2:1	34.18	0.465	0.480	975
	3:1	33.55	0.667	0.709	1110
	4:1	31.22	0.476	0.491	1250
Volume of vegetable oil (ml)	300	32.99	0.667	0.709	1330
	400	33.29	0.705	0.750	1440
	500	30.04	0.793	0.830	1510
Stirring speed (rpm)	75	31.22	0.529	0.546	1375
	100	31.43	0.675	0.700	1295
	150	31.58	0.667	0.709	1250

one sieve but were retained on the other were collected and weighed and the distribution was analyzed based on the weight fraction on each sieve. The average diameter was also calculated

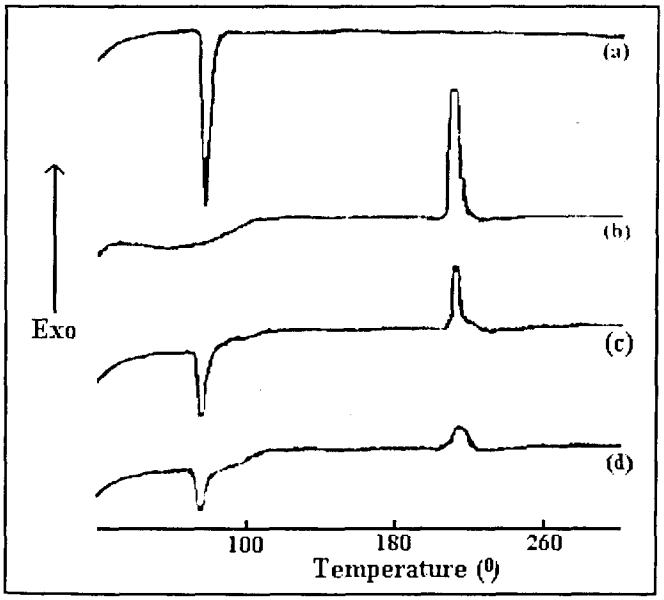

Fig. 1: DSC thermograms of carrageenan agglomerates.

DSC thermograms of ibuprofen (a), blank carrageenan agglomerates (b), ibuprofen - carrageenan physical mixture (4:1) (c), ibuprofen - carrageenan agglomerates (4:1) (d).

Differential scanning calorimetry:

The DSC analysis was carried out to identify the crystalline form of the drug in agglomerates. The DSC analysis of pure drug, blank agglomerates and drug-loaded agglomerates were carried out using Perkin Elmer DSC; Model-7. Blank carrageenan agglomerates and drug-loaded agglomerates were triturated to get a finely divided powder. This powder was passed through 100 # sieve. Similarly pure drug was also passed through 100 # sieve. Samples (2-8 mg) were accurately weighed and heated in sealed aluminum pans at a rate of 10°/min between 50 to 250° temperature range under a nitrogen flow of 40 ml/min.

X-ray powder diffractometry:

The crystalline form of the drug dispersed in the crust of the agglomerates was analyzed by X-ray powder diffractometry. Studies were carried out to investigate the effect of agglomeration process on crystallinity of the drug. Powder X-ray diffraction patterns were recorded on a Jeol PW 17291 powder X-ray diffractometer using Ni-filtered, CuKα radiation, a voltage of 35 Kv and a current of 25 mA. The scanning rate employed was 1°/min over the 10-40° 2θ range. The XRD patterns of Ibuprofen raw material, empty carrageenan agglomerates and drug-loaded agglomerates were recorded. Agglomerates were triturated to get fine powder before taking the scan.

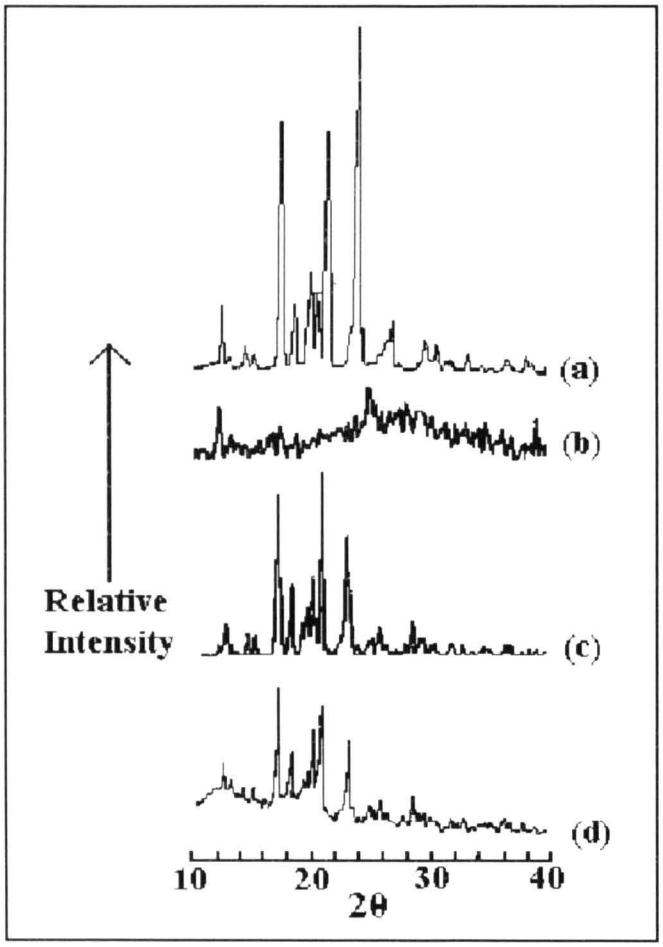

Fig. 2: XRD spectra of carrageenan agglomerates.

XRD spectra of ibuprofen (a), blank carrageenan agglomerates (b), ibuprofen - carrageenan physical mixture (4:1) (c), ibuprofen - carrageenan agglomerates (4:1) (d).

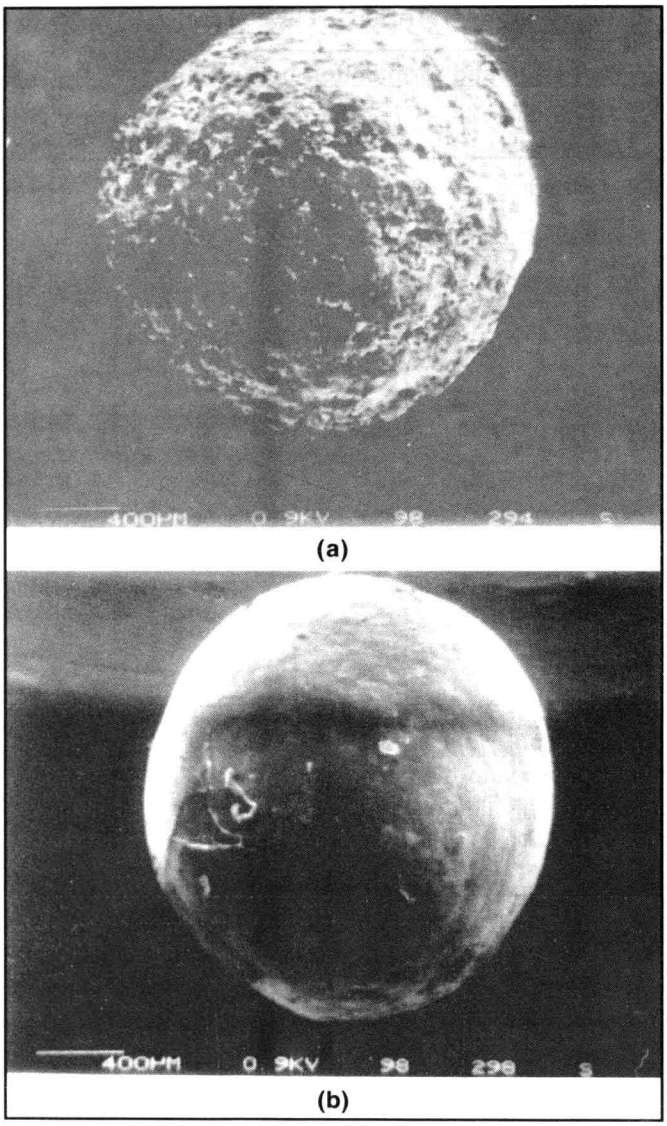

Fig. 3: SEM photographs of carrageenan agglomerates.

SEM photographs of carrageenan agglomerates with (a) and without (b) drug.

Micromeritic properties of agglomerates:

The flow and packing properties were investigated by measuring the angle of repose and tapped densities, respectively. The surface topography of the agglomerates was examined by scanning electron microscopy using a Cambridge stereoscan-150 scanning microscope. Prior to examination, samples were gold sputter-coated to render them electrically conductive.

Measurement of drug release rate from agglomerates:

The *in vitro* release profile of the drug-loaded agglomerates was obtained using USP XXIII paddle type dissolution apparatus. Accurately weighed agglomerates (equivalent to 200 mg of the drug) were gently spread over the surface of dissolution medium. The dissolution media used was pH 7.2 phosphate buffer maintained at 37±0.5°. A stirring speed of 100±1 rpm was used. Aliquots were withdrawn at regular pre-determined intervals and analysed spectrophotometrically at a wavelength of 264 nm using Milton Roy UV/Vis Spectrophotometer. The dissolution studies were repeated three times and the mean values are plotted as percent cumulative release versus time.

RESULTS AND DISCUSSION

The effects of various process and formulation parameters on the drug entrapment efficiency and particle

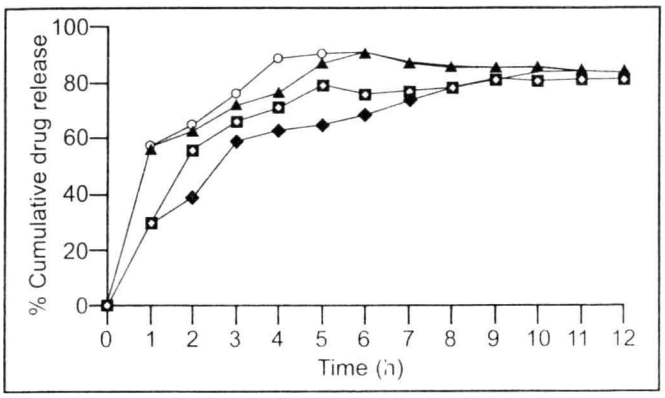

Fig. 4: % Cumulative drug release at different time interval from drug loaded agglomerates.

Effect of drug polymer ratio, 1:1 (-0-), 2:1 (-▲-), 3:1 (-□-) and 4:1 (-◆-) on the cumulative release of drug from carrageenan agglomerates. Speed of agitation 150 rpm; volume of sunflower oil 300 ml and temperature of oil; 2-5°, were kept same for all these batches.

size are shown in Table 1 and Table 2, respectively. Increasing the speed of agitation increased the entrapment efficiency. This may be due to increase in surface area of particles during stirring at high speed. Good entrapment efficiency was also achieved at higher drug-polymer ratio (4:1) due to increase in concentration of drug. Entrapment efficiency of drug and agglomerate size was found to be decreased with increasing stirring time from 2-8 h. This may be attributed to the increased collision of agglomerates while stirring for a longer period of time. The volume of oil does not have any impact on entrapment efficiency of ibuprofen agglomerates. As volume of oil increases, size of

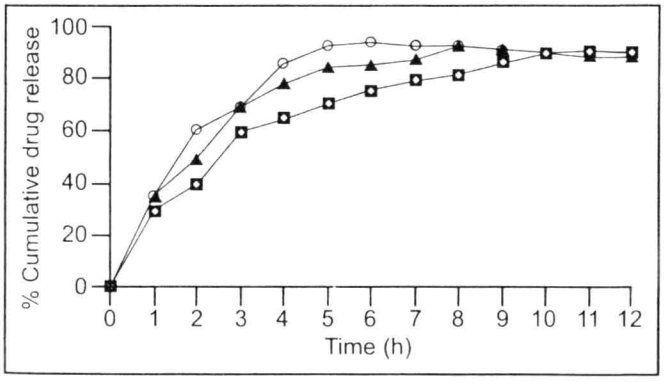

Fig. 5: Comparison of *in vitro* release profile of drug from carrageenan agglomerates using varied amounts of sunflower oil.

300ml (-□-), 400ml (-o-), 500 ml (-▲-). Speed of agitation 150 rpm; polymer drug ratio 1:4 and temperature of oil = 2-5°, were kept same for all these batches.

agglomerates increases. This may be attributed to less collision between the agglomerates while stirring due to higher viscosity of the system. The extent of loading appears to influence the particle size distribution of agglomerates. When the loading is high, the proportion of larger particles formed is also high. The viscosity of the polymer solution at such high drug loadings is very high and is responsible for the formation of large agglomerates. The micromeritic properties of the agglomerates are shown in Table 2. The flow properties, represented in terms of angle of repose of the agglomerates indicate that the drug-loaded agglomerates had good flow properties.

The drug could be either dispersed in crystalline/ amorphous form or may be dissolved in the polymeric matrix during the agglomerate preparation[8,9]. Also, any abrupt or drastic change in the thermal behavior of either the drug or polymer may indicate a possible drug-polymer interaction. The thermal curves of pure components and of the drug-polymer micropellets are presented in fig. 1. A sharp endotherm was observed for ibuprofen at 74° corresponding to its melting point. In case of carrageenan, exothermic peak was observed in the temperature range of 204.13 to 216.56° (Tpeak =211.65°). In the case of physical mixture (drug: polymer 4:1 ratio), drug endothermic peak was observed at 72.05° corresponding to its melting transition and carrageenan exotherm was seen at 210.89°. The same thermal behavior was observed in drug loaded, i.e. ibuprofen-carrageenan agglomerates showing thermal peaks at 70.73° for drug and 210.34° for polymer. This clearly indicated that there was no drug polymer interaction and that the drug was dispersed in the polymer matrix in the crystalline state and not dissolved in the polymer matrix.

The X-ray powder diffraction patterns of agglomerates along with those of physical mixtures and raw crystals of drug and polymer are shown in fig. 2. It was found that ibuprofen in the agglomerates was unchanged in crystalline form. The reduced diffraction intensity and broadening of peaks suggests that some drug has been dispersed uniformly in the molecular level like a solid dispersion in the polymer matrix of the agglomerates[10].

Scanning electron micrographs of the surface of the agglomerates is as shown in fig. 3. This revealed that the agglomerates are spherical in shape and had a rough surface due to higher concentration of drug in the agglomerates. This finding explains the fact that the crystallinity of the ibuprofen agglomerates was higher as

revealed by the DSC and X-ray diffraction studies.

Factors such as microsphere size, drug loading, polymer composition and molecular weight govern the drug release from microspheres[11,12]. At lower drug polymer ratios, the mean particle size of the microspheres was less than that at higher drug polymer ratios. Therefore, the drug release from microspheres prepared at lower drug polymer ratios was faster than those prepared at higher drug polymers ratios due to the small size of microspheres which provide large surface area for faster drug release as presented in fig. 4. The effect of stirring speed and stirring time during preparation of ibuprofen agglomerates on the *in vitro* drug release was not significantly different. The volume of sunflower oil as the oily phase plays an important role in the cumulative release of ibuprofen from agglomerates as shown in fig. 5. This can be attributed to the change in viscosity of the oily phase, which in turn controls the agglomerate size.

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