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Preparation, Characterization and *In-vitro* Evaluation of Microcapsules for Controlled Release of Diltiazem Hydrochloride by Ionotropic Gelation Technique

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ABSTRACT

The problems of frequent administration and variable low bioavailability after oral administration of conventional dosage forms of diltiazem can be attenuated by designing it in the form of microcapsules which would facilitate intimate contact with the absorption surface and thereby improve and enhance the bioavailability. Diltiazem-loaded microcapsules were successfully prepared by ionotropic gelation technique employing Sodium carboxy methylcellulose, Xanthan gum as rate controlling polymers and Aluminium chloride as cross linking agent. Microcapsules obtained were discrete, spherical, free flowing and showed a maximum encapsulation efficiency of 91.20 ± 0.08%. Particle size of the microcapsules was found to be in the range of 1009 – 1311 µm. Interaction studies performed using FTIR spectroscopy revealed that there were no drug and polymer interactions. The drug remained dispersed in the polymer matrix in amorphous state, which was confirmed by X-ray diffraction analysis. The *in vitro* drug release follows matrix-diffusion controlled release and the release mechanism was non-Fickian type controlled by swelling and relaxation of polymer. There was no significant change in drug content and cumulative drug release of drug-loaded microcapsules stored at different storage condition after 90 days. From the study, it was concluded that diltiazem loaded microcapsules could be successfully prepared by ionotropic gelation technique with high entrapment efficiency and prolonged release characteristics.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process (Manjanna *et al.*, 1999).

Controlled drug delivery containing polymeric carriers has gained increased interest in last two decades, because they can be fabricated into films, rods and microparticles. Formulation of multiunit sustained release dosage forms like microcapsules; microbeads with synthetic polymers require organic solvents. Currently, there is a trend to restrict or even to eliminate the use of organic solvents in pharmaceutical formulations for various reasons (Belgamwar *et al.*, 2009). Consequently, extensive research efforts have been concentrated on natural polymers as encapsulating materials as they are derived from natural sources, easily available, qualified for a number of chemical modifications and do not require organic solvents for processing (Shirwaikar *et al.*, 2008). Diltiazem hydrochloride (DH) is an L-type calcium channel blocking agent used for the treatment of angina pectoris, hypertension and arrhythmias. The conventional tablet and capsule is administered 3 or 4 times a day due to its short biological half-life of about 3-6 hours. The problems of frequent administration and variable low bioavailability (30-60%) after oral administration of conventional tablet or capsules have been attenuated by designing diltiazem in the form of sustained release tablet or capsules (Das and Maurya, 2008).

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However, such single unit sustained release tablets could be disastrous if they fail to release the drug at the desired rate and in the desired amount also, sustained release forms are administered two times a day due to its limited residence time in the gastrointestinal tract (Akbuga and Durmaz, 1994).

Amongst the various approaches available, multiunit microparticulate drug delivery systems (ex: microcapsules) is gaining importance as they can be widely distributed throughout the gastrointestinal tract providing a possibility of achieving long lasting and reliable release of drug at desired rate. Unwanted intestinal retention of the polymeric material and local irritation which may occur with non-disintegrating polymeric matrix tablets, can also be avoided. Microcapsules facilitate intimate contact with the absorption surface and thereby improving and enhancing the bioavailability (Das and Senapati, 2008).

Xanthan gum (XG), a high molecular weight exopolysaccharide produced by *Xanthomonas campestris*. In addition to its use in food products without specific quantity limitations, it is being widely used in pharmaceutical products because of its safety reports (Katzbauer, 1998). Controlled-release tablets of diltiazem hydrochloride prepared using xanthan gum have been reported (Peh and Wong, 2000). Carboxymethylcellulose sodium (Sodium CMC), the sodium salt of a polycarboxymethyl ether of cellulose is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties (Rowe *et al*., 2009)

The objective of the present study was to develop microcapsules of Dilitiazem hydrochloride by ionotropic gelation technique employing Xanthan Gum and Sodium carboxymethyl cellulose as rate controlling polymers. The effect of factors such as drug concentration, polymer ratios, concentration of crosslinking agent (Aluminium chloride) and curing time on the drug encapsulation efficiency and drug release characteristics were studied**.**

MATERIALS AND METHODS

Diltiazem Hydrochloride was obtained as a generous gift sample from Shrushti Pharmaceuticals, Bangalore, Xanthan gum and sodium carboxymethylcellulose medium viscosity grade (200-400 cPs) were obtained from Kachabo Gums (Mumbai) and SD Fine chemicals Ltd. (Mumbai) respectively, and aluminum chloride Hexahydrate was purchased from Thomas Baker chemicals Limited (New Delhi). All other reagents used were of analytical grade.

Preparation of beads

Microcapsules containing DH were prepared by ionotropic gelation technique (Chowdary and Srinivasa Rao, 2003a) employing Sodium CMC in combination with XG as coat material. Sodium CMC and XG were dissolved in purified water to form a homogeneous polymer solution. The active substance, DH, was added to the polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added manually dropwise into aluminium chloride solution through a syringe with a needle of size no. 23. The added droplets were retained in the aluminium chloride solution for the defined period of time to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules were collected by decantation, and the product thus separated was washed repeatedly with water and dried at 40°C for 12 hours. The microcapsules prepared along with their coat composition are listed in Table 1.

Table. 1: Composition of Diltiazem hydrochloride microcapsule formulation.

Formulation Code	Drug (%w/v)	Xanthan Gum (%w/v)	Sodium CMC (% w/v)	Crosslinking agent (% w/v)	Curing Time (minutes)
F1	0.5	1.5	1.5	20	10
F2	1	1.5	1.5	20	10
F3	1.5	1.5	1.5	20	10
F4	1	1.5	1.5	10	10
F5	1	1.5	1.5	15	10
F6	1	1.5	1.5	20	15
F7	1	1.5	1.5	20	20
F8	1	2.0	1.0	20	10
F9	1	1.0	2.0	20	10

Characterization and Evaluation of Microcapsules

Percentage Yield

The practical percentage yield (Swamy and Abbas, 2012) was calculated from the weight of dried microcapsules recovered from each batch in relation to the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

% Yield = Practical mass (microcapsules) / Theoretical mass (Polymer + drug) X 100

Estimation of drug content and encapsulation efficiency

For determination of the drug content, microcapsules equivalent to 100 mg of DH were crushed in a glass mortar and pestle and the powdered microcapsules were suspended in 100 ml of phosphate buffer pH 7.4. After 24 h, the solution was filtered, 1 ml of the filtrate was pipetted out and diluted to 10 ml and analyzed for the drug content using Shimadzu-1700 (Japan) UV Visible spectrophotometer at 236 nm (Nappinnai and Kishore, 2007). The drug content was computed using a calibration curve (R^2 = 0.9998) prepared using solutions with concentrations of 2 to 16 mg/mL of DH. The drug encapsulation efficiency (Masareddy, *et al*., 2011) was calculated using the following formula:

% drug encapsulation efficiency

= Practical drug content / Theoretical drug content X 100

Particle Size Analysis

The particle size determination of DH-loaded microcapsules was carried out using optical microscopy along with a stage micrometer having an accuracy of 0.01 mm. A suspension of microcapsules in liquid paraffin was prepared in a beaker and then one drop of this was dropped on a clean glass slide and covered with a cover slip. The average sizes of 100 microcapsules were determined for each formulation using the calibration factor.

The average particle size of the microcapsules was determined by using Edmondson's equation (Swamy and Abbas, 2011).

$D_{mean} = \Sigma nd / \Sigma n$

Where, n = Number of microcapsules checked; d = Mean size range

Shape and Surface Morphology:

The shape and surface characteristics of the drug loaded microcapsules were evaluated by means of scanning electron microscopy (JEOL JSM - 6363, Japan). The samples were prepared by gently sprinkling the microcapsules on a double adhesive tape, which is stuck to an aluminium stub. The stubs were then coated with gold using a sputter coater (JEOL Fine coat JFC 1100E, ion sputtering device) under high vacuum and high voltage to achieve a film thickness of 30 nm (Swamy and Abbas, 2011). The samples were then imaged using a 20 KV electron beam.

Fourier Transform Infra red analysis (FTIR)

The IR analysis (Mandal, *et al*., 2010) of pure drug and drug-loaded microcapsules were analyzed with FTIR spectrophotometer (Shimadzu FTIR-8400, Japan). All the samples were crushed with potassium bromide to get pellets at 600kg cm^{-2}. Spectral scanning was done in the range of 400-4000 cm^{-1}.

Differential Scanning Calorimetry (DSC)

The DSC analysis (Das and Maurya, 2009) of pure DH, blank microcapsules and drug-loaded microcapsules were carried out in the heating range of 25 – 300^0C at a rate of 10^0C/min using differential scanning calorimeter (DSC 823, Mettler Toledo, Switzerland).

X-ray diffraction analysis (XRD)

The qualitative X-ray diffraction studies (Sultana *et al*., 2009) were performed using an X-ray diffractometer (P Analytical, X Pert Pro). Drug loaded and blank microcapsules were scanned from 0-60^0 diffraction angle (2θ) range under the following measurement conditions: source, nickel filtered Cu-Kα radiation; voltage 40 Kv; current 30mA; scan speed 0.05/min. microcapsules were triturated to get fine powder before taking the scan. X-ray diffractometry was carried out to investigate the effect of microencapsulation process on crystallinity of the drug.

Degree of Swelling

Swellability of the microcapsules was determined by allowing the microcapsules to swell in the phosphate buffer pH 7.4. 100 mg of accurately weighed microcapsules were immersed in little excess of phosphate buffer pH 7.4 for 24 hours and washed thoroughly with deionised water and blotted with filter paper to remove excess surface liquid (Jain *et al*., 2007). The % swelling was arrived at using the following formula:

Degree of Swelling = Ws –Wo / Wo

Where, Wo is the weight of microcapsules before swelling and Ws is the weight of microcapsules after swelling.

***In vitro* dissolution study**

The *in vitro* release of diltiazem hydrochloride from the microcapsules was carried out in basket type dissolution tester USP XXIII, TDT-08L, containing 900 ml of pH 1.2 buffer for the first 2 hrs and in 7.4 pH phosphate buffer for the next 10 hrs. An accurately weighed quantity of the microcapsules (100 mg) was stirred in 900 ml of the dissolution media at agitation speed of 100 rpm and temperature of bath was maintained at 37 ± 0.5°C (Patil et al., 2012; Chowdary and Srinivasa Rao, 2003b). At preset time intervals, 10 ml aliquots were withdrawn and replaced with an equal volume of fresh dissolution media. After suitable dilution, the Samples were analyzed spectrophotometrically at 236 nm using Shimadzu-1700 (Japan) UV Visible spectrophotometer.

***In Vitro* Drug Release Kinetics**

For understanding the mechanism of drug release and release rate kinetics of the drug from the dosage form, the data obtained was analysed with software (PCP - Disso V2.08) equipped with zero order, first order, Higuchi matrix and Korsmeyer – Peppas model kinetics (Swamy *et al*., 2010; Costa *et al*., 2001) By analyzing the R values, the best fit model was found.

Stability studies

The drug loaded microcapsules were stored at various storage conditions (room temperature Stability (25^0C ± 2^0C / 60% RH ± 5% RH) and accelerated stability (40^0C ± 2^0C / 75% RH ± 5% RH) in airtight sealed vials for three months using Programmable environmental test chambers (REMI Instruments ltd.). Samples were analyzed at the end of 30, 60 and 90 days and they were evaluated for % drug content and *in vitro* dissolution studies (Sultana *et al*., 2009).

RESULTS AND DISCUSSION

Diltiazem Hydrochloride loaded microcapsules of Xanthan gum and Sodium CMC were prepared by ionotropic gelation technique employing Aluminium chloride as cross linking agent. The obtained microcapsules were discrete, spherical in shape and freely flowing.

It was observed that as the drug to polymer concentration increases, the product yield also increases. The low percentage yield in some formulations may be due to microcapsules lost during the washing process. The percentage yield was found to be in the range of 81.58 to 95.50%. The % Drug encapsulation efficiency of Diltiazem Hydrochloride in the microcapsules is given in the Table 2, which ranged from 67.86 ± 0.15 % to 91.20 ± 0.08 %.

As the drug concentration was increased from 0.5%w/v to 1.5% w/v in formulations F1 to F3, % drug encapsulation efficiency decreased in the same concentration range. The decrease in entrapment efficiency with increase in drug concentration could be related to the increased extent of drug diffusion to the external phase due to greater flux at higher drug content during the microcapsule formation process. Increase in the concentration of

crosslinking agent from 10% w/v to 20% w/v in formulations F4 to F6 led to an increase in the drug encapsulation efficiency which may be explained by the increase in the gel strength as the aluminium ion increased. Consequently the cross linking of the polymers and compactness of the formed insoluble matrices also increased. This would result in more drug encapsulation in the microcapsules. However, further increase in concentration of crosslinking agent above 20%w/v did not enhance the drug encapsulation due to possible saturation of aluminium binding sites of the polymer. On the other hand, increase in curing time from 10 to 20 minutes in formulations F6 to F8, did not have a significant effect on % drug encapsulation efficiency.

The mean particle size of the prepared microcapsules in presented in Table 2. The average microcapsule size was found to be in the range of 1009 to 1311µm. It was noticed that as, the concentration of drug was increased particle size also increased which could be attributed to the increased drug content of the dispersion droplet at higher drug concentration. Increase in Aluminium chloride concentration led to a decrease in the mean particle size. The higher amount of CLA appears to favour better cross linking forming spherical microcapsules. Increase in curing time from 10 to 20 minutes increases the degree of congealing or rigidization of the polymer, which ultimately results in shrinking of the particles, leading to decrease in particle size.

The photographs of the optimized formulation (F2) taken by scanning electron microscope are depicted in the Figure 1. The SEM photographs revealed that the microcapsules were discrete and spherical in shape with a rough outer surface morphology which could be because of the surface association of the drug with the polymer. The pores on microsphere surface could help in drug release by diffusion mechanism.

FT-IR spectra of pure diltiazem hydrochloride and drug loaded microcapsules were compared and shown in Figure 2. The FT-IR spectra of the drug loaded microcapsules showed the characteristic peaks of the pure drug indicating that there was no interaction between the drug and polymers.

DSC study of diltiazem hydrochloride, blank microcapsules and drug-loaded microcapsules were compared (Figure 3) to study the stability of the drug during the formulation and any abrupt or drastic change in the thermal behaviour of either the drug or polymers. DSC curve of diltiazem hydrochloride showed a sharp endothermic peak at 215^{o}C, corresponding to its melting point. The drug-free beads have shown an endothermic peak at 117^{o}C and 180 ◦C indicating melting temperature of the polymer, whereas drug-loaded beads showed an endothermic peak at 121^{o}C. The endothermic peak of diltiazem hydrochloride was not distinctive indicating that the drug was molecularly dispersed in an amorphous state in the polymer matrix, which was further confirmed by X-ray diffraction study.

The X-ray diffractograms of pure diltiazem hydrochloride and drug-loaded microcapsules are shown in Figure 4. Diltiazem has shown characteristic intense peaks between the 2θ of 8^{o} and 16^{o} due to its crystalline nature. Whereas, in case of drug loaded beads, no intense peaks related to drug were noticed between the 2θ of 8^{o} and 16^{o}. This indicates the amorphous dispersion of the drug after entrapment into microcapsules.

The dynamic swelling study of the prepared microbeads was carried out in phosphate buffer pH 7.4 and the results are presented in Table 2. The swelling of microbeads depends upon the concentration of polymers and extent of $AlCl_3$ cross linking in the beads. The swelling of the microcapsules increased with an increasing amount of polymers and swelling decreased with an increasing amount of $AlCl_3$.

The *in-vitro* drug release study was performed using dissolution rate test apparatus USP-XXIII in 0.1 N HCl (pH 1.2) for initial 2 hours followed by phosphate buffer (pH 7.4) for remaining 10 hours. The drug release behaviours are shown in Figure 5 - 7.

The result in figure 5 reveals that increase in the drug concentration while keeping the polymer constant did not have any significant effect on the *in vitro* drug dissolution profile as more than 95% of the drug was released at the end of 12 hours. The results of the dissolution study in figure 6 indicated that the amount of drug release significantly decreased with an increase in the concentration of the cross linking agent and curing time. It can be attributed to increase in the extent of cross linking in the microcapsules with increase in the amount of crosslinking agent. The Al^{3+} crosslinked microcapsules form three dimensional bonding structure with the Sodium CMC inside the microcapsules. This three dimensional bonding results in extended crosslinking through the whole microcapsule producing hard microcapsules with lower water uptake and thus leading to slow removal of drug in the phosphate buffer. The drug dissolution profile in figure 7 did not show any significant effect of the different polymer ratios on the *in vitro* drug dissolution.

The best-fitted model with higher correlation coefficient was shown in the Table 3. In all the cases, the R values of Higuchi matrix model were close to 1. The diffusion coefficient (n) values ranged between 0.4490 to 0.8911. Since the R values of Higuchi matrix were close to 1, the drug release follows matrix diffusion-controlled kinetics and the plot shown in Figure 8 revealed linearity; hence it was concluded that diffusion was the main mechanism of drug release from the microcapsules. Further, the observed diffusion coefficient values are indicative of the fact that the drug release from the formulation follows non-Fickian transport mechanism controlled by swelling and relaxation of polymer.

The stability data showed that there was no change in the appearance of the microcapsules indicating that the formulations were stable at different conditions of storage. The stability study was performed for the prepared formulation as per the ICH guidelines and it showed that the formulation F2 was stable, with no physical change and also there was no significant reduction in drug content.

Thus, we may conclude that, the drug does not undergo degradation on storage.

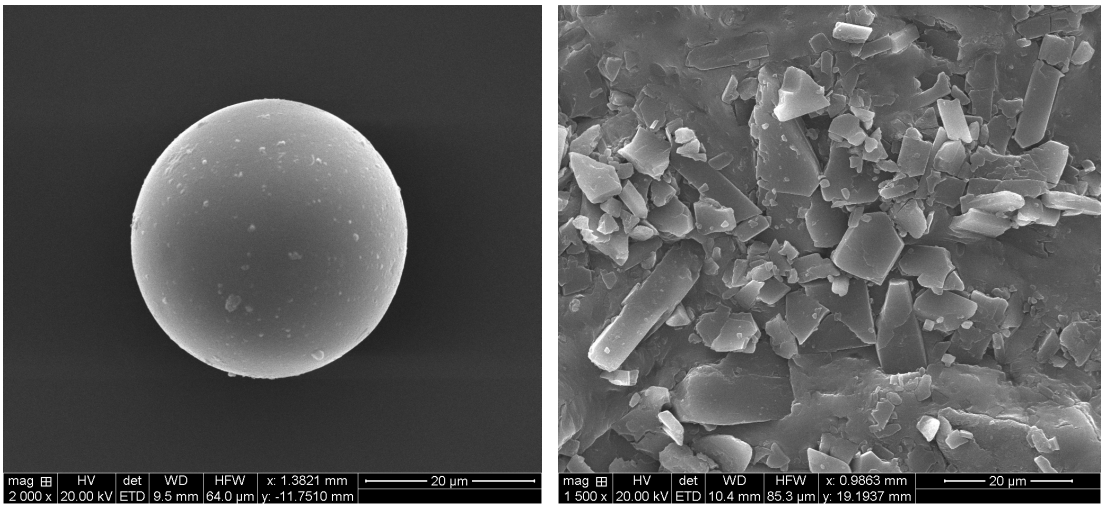
Table. 2: Characteristics of the prepared microcapsules.

Formulation Code	% Yield	% Encapsulation efficiency*	Particle size (µm)*	% swelling*
F1	85.76	70.33 ± 0.05	1204 ± 1.89	1.116 ± 0.015
F2	81.58	74.26 ± 0.08	1120 ± 1.45	1.121 ± 0.021
F3	83.50	67.86 ± 0.15	1064 ± 1.36	1.113 ± 0.012
F4	87.29	77.13 ± 0.45	1009 ± 2.36	1.114 ± 0.060
F5	89.59	82.93 ± 0.75	1311 ± 4.56	1.002 ± 0.015
F6	91.05	86.67 ± 0.45	1277 ± 1.87	0.996 ± 0.022
F7	95.50	91.20 ± 0.08	1259 ± 3.44	1.120 ± 0.016
F8	88.75	85.80 ± 0.42	1250 ± 1.75	1.116 ± 0.024
F9	88.95	83.33 ± 0.75	1246 ± 1.89	1.106 ± 0.033

*Data are expressed as mean ±SD. n = 3

Table. 3: *In vitro* release data fitting into various mathematical models.

		F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order	R	0.8854	0.9013	0.9239	0.9441	0.9191	0.9133	0.9421	0.9579	0.9688
	k	0.1432	0.1264	0.1204	0.1069	0.1326	0.1429	0.1311	0.1212	0.1172
First order	R	0.8892	0.9438	0.9495	0.9646	0.9542	0.942	0.9427	0.9489	0.9539
	k	-0.0012	-0.0011	-0.0012	-0.0011	-0.0015	-0.0012	-0.0012	-0.0011	-0.0012
Matrix	R	0.9712	0.9731	0.9755	0.9728	0.9811	0.9822	0.9865	0.9845	0.9851
	k	0.3321	0.3015	0.2883	0.255	0.3012	0.3451	0.3022	0.2872	0.2579
Hixon-Crowell	R	0.8865	0.9436	0.9493	0.9645	0.9466	0.8859	0.9438	0.9489	0.9658
	k	-0.0005	-0.0004	-0.0004	-0.0004	-0.0003	-0.0005	-0.0005	-0.0004	-0.0004
Peppas	R	0.9561	0.9765	0.9625	0.9707	0.9612	0.9556	0.9757	0.9682	0.9713
	k	0.2692	0.1573	0.1555	0.1305	0.1654	0.2689	0.157	0.1566	0.1308
	n	0.4490	0.6621	0.6984	0.8125	0.6971	0.6655	0.8123	0.8891	0.8469



(a) **(b)**

Fig. 1: Scanning electron microphotographs of formulation F2 (a) and surface of the microcapsule (b).

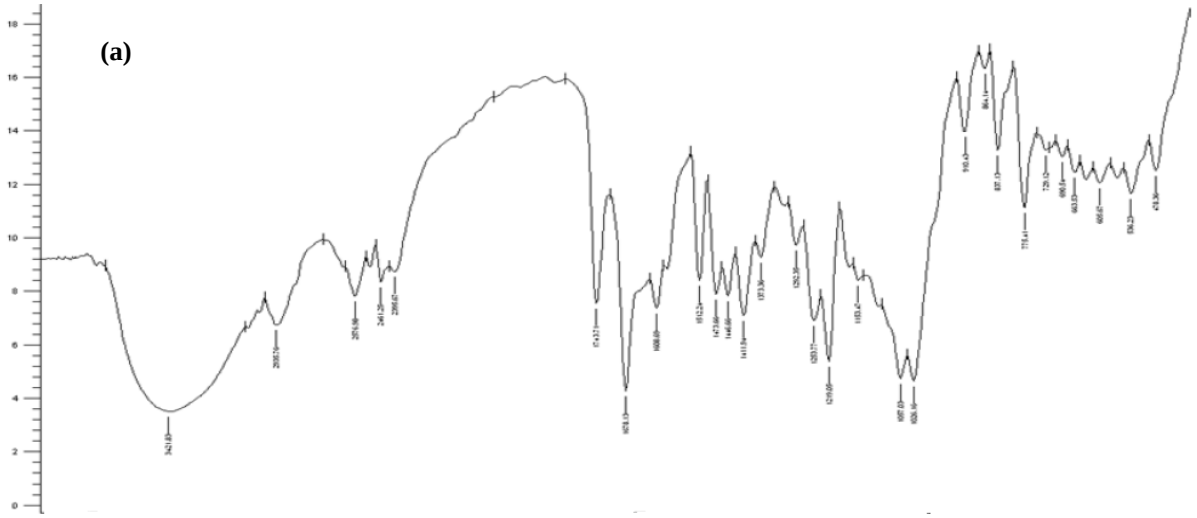


Fig. 2:…

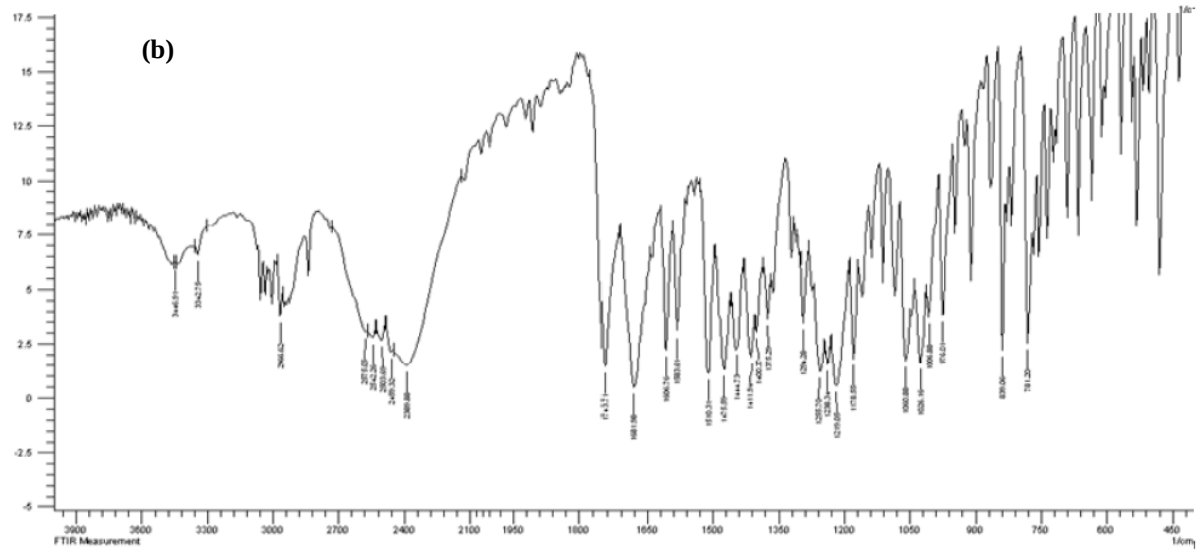


Fig. 2: FT-IR spectrogram of drug loaded microcapsule (a) and Diltiazem Hydrochloride (b).

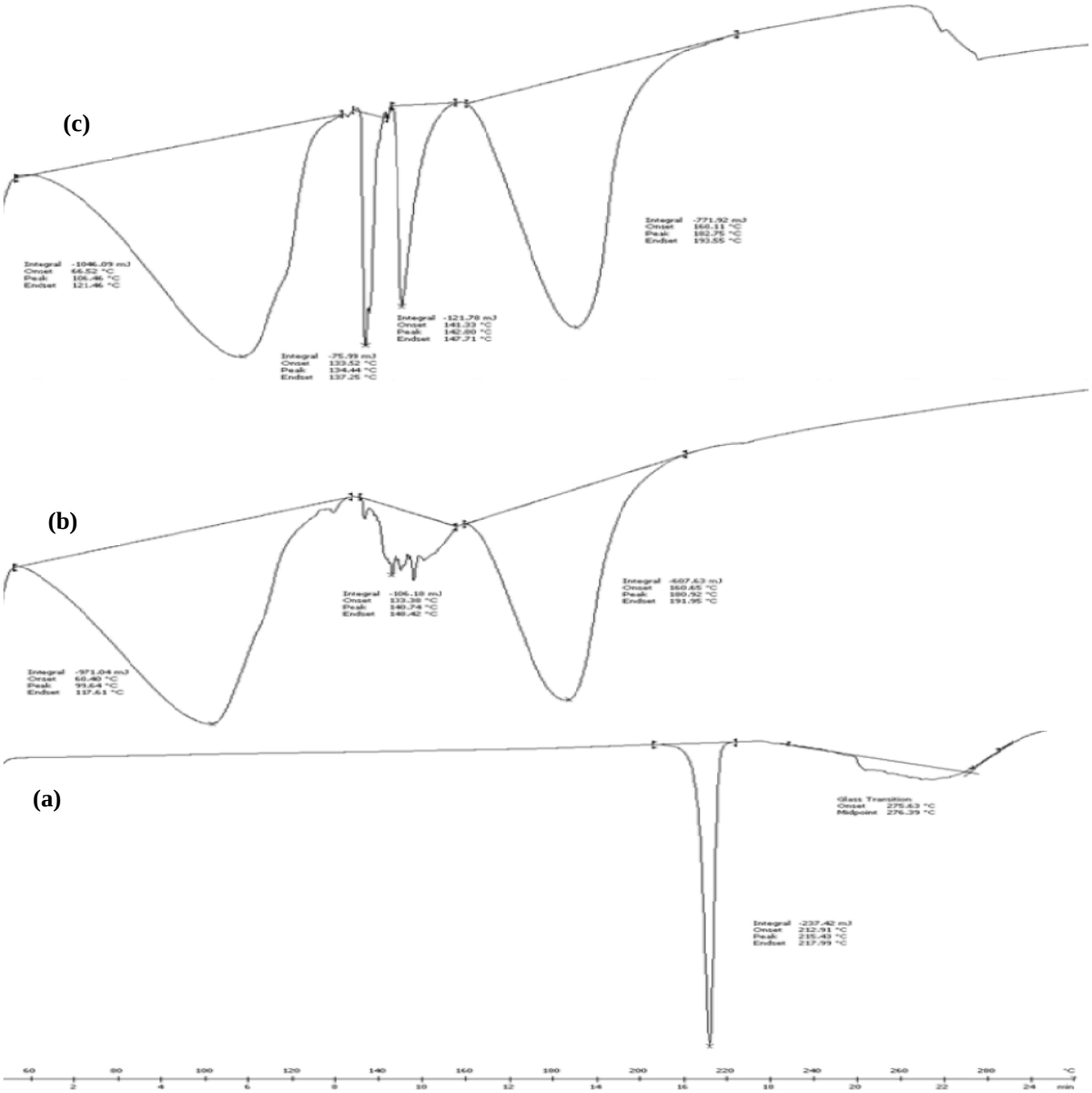


Fig. 3: DSC Thermogram of pure drug (a), blank microcapsules (b) and drug loaded microcapsule (c).

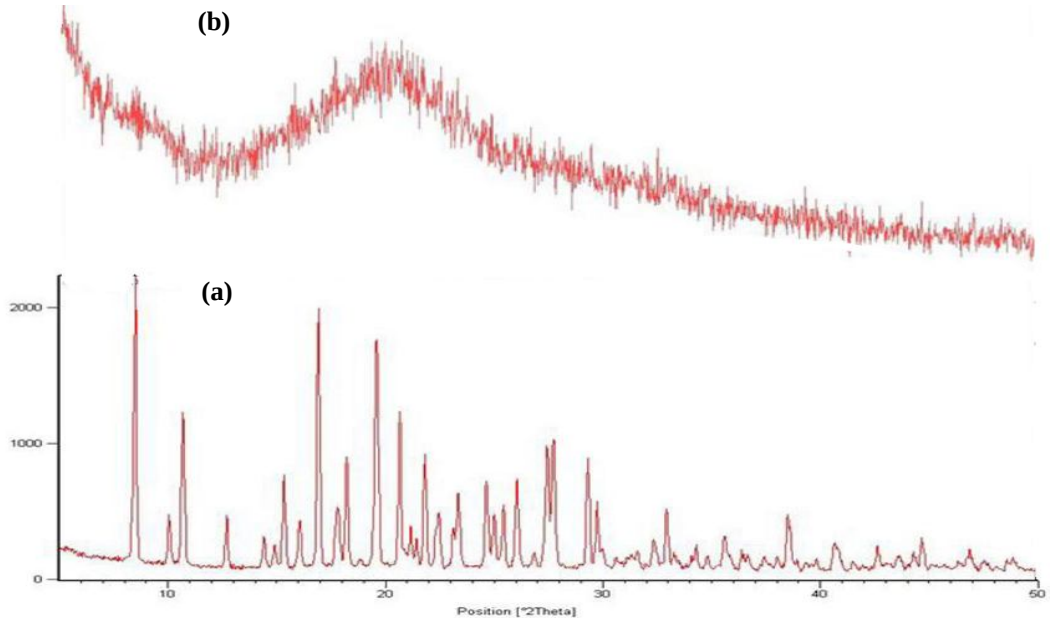


Fig. 4: X-ray diffractograms of pure drug (a) and drug loaded microcapsule (b).

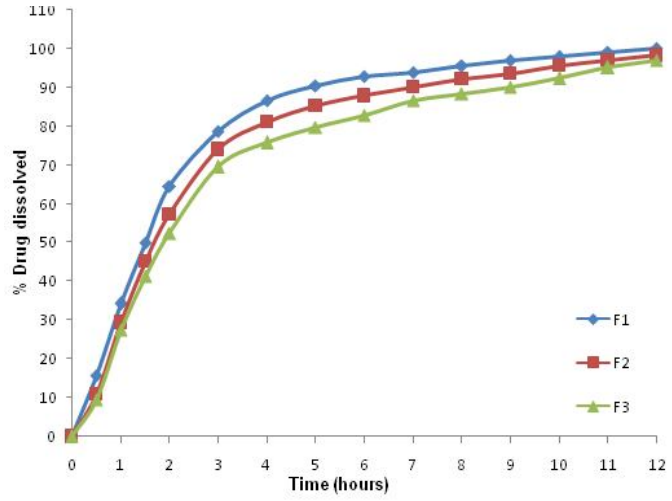


Fig. 5: *In vitro* drug dissolution from formulation F1, F2 and F3.

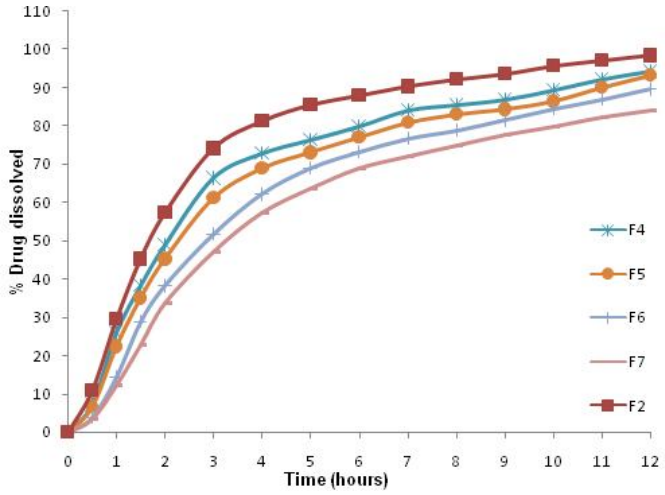


Fig. 6: Effect of cross linking agent concentration and curing time on *In vitro* drug dissolution from formulation F2, F4, F5, F6 and F7.

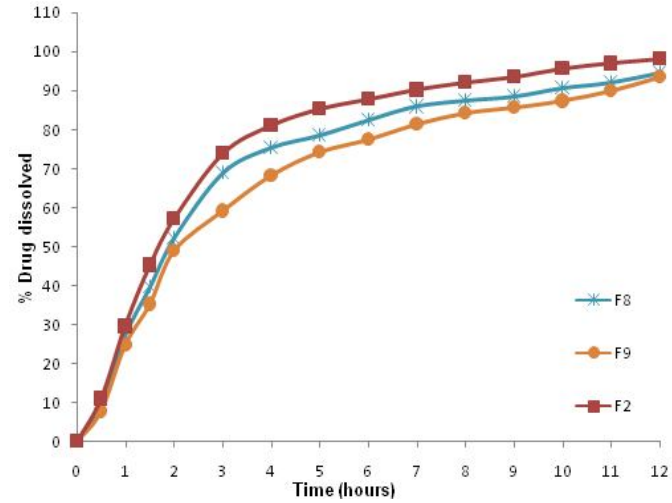


Fig. 7: *In vitro* drug dissolution from formulation F2, F8 and F9.

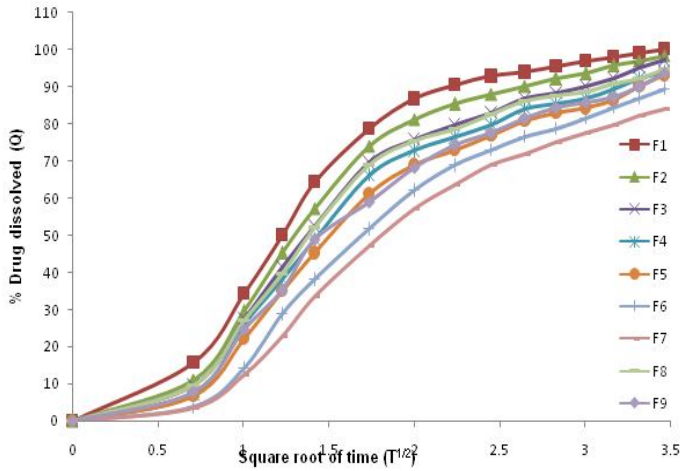


Fig. 8: Higuchi plot for different microcapsule formulations (F1- F9).

CONCLUSION

Thus, large spherical microcapsules with a coat consisting of Sodium CMC and Xanthan gum for the controlled release of diltiazem hydrochloride with higher encapsulation efficiency were successfully prepared by ionotropic gelation technique. Diltiazem hydrochloride release from the microcapsules was found to be slow, controlled and extended over a period of 12 hours. The drug release was found to be diffusion controlled which followed Higuchi matrix kinetics and mechanism was non-fickian type controlled by swelling and relaxation of polymer chain.. Thus the results of the present study clearly indicated a promising potential of mucoadhesive drug delivery system in the delivery of drugs with lower half lives and less bioavailability.These microcapsules are, thus, suitable for oral controlled release of Diltiazem hydrochloride.

REFERENCES

Akbuga J, Durmaz G. preparation and evaluation of cross linked chitosan microspheres containing furosemide. Int. J. Pharm. 1994; 111: 217-222.

Belgamwar V, Shah V, Surana SJ. Formulation and Evaluation of Oral Mucoadhesive Multiparticulate System Containing Metoprolol Tartarate: An *In Vitro – Ex Vivo* Characterization. Curr. Drug Deliv. 2009; 6: 113-121.

Chowdary KPR and Srinivasa Rao Y. Design and *In Vitro* and In Vivo Evaluation of Mucoadhesive Microcapsules of Glipizide for Oral Controlled Release: A Technical Note. AAPS PharmSciTech. 2003a; 4: article 39 (1-6).

Chowdary KPR and Srinivasa Rao Y. Preparation and evaluation of mucoadhesive microcapsules of Indomethacin. Saudi Pharmaceutical journal. 2003b; 11: 97-103.

Costa P, Manuel J, Lobo S, Modelling and comparision of dissolution profiles. Eur. J. Pharm. Sci. 2001; 13: 123-133.

Das MK and Maurya DP. Evaluation of diltiazem hydrochloride loaded mucoadhesive microspheres prepared by emulsification internal gelation technique. Acta Poloniae Pharmaceutica -Drug Research. 2008; 65: 249-259.

Das MK and Senapati PC. Furosemide-loaded alginate microspheres prepared by ionic cross linking technique: Morphology and release characteristics. Indian J. Pharm. Sci. 2008; 70: 77-84.

Das MK and Maurya DP. Microencapsulation of water –soluble drugs by emulsification internal gelation technique. Indian J. Pharm. Educ. Res. 2009; 43: 28-38.

Jain SK, Jain NK, Gupta Y, Jain A, Jain D and Chaurasia M., Mucoadhesive chitosan microspheres for non-invasive and improved nasal delivery of Insulin. Indian J. Pharm. Sci. 2007; 69: 498-504.

Katzbauer B. Properties and applications of Xanthan Gum. Polym. Degrad. Stabil. 1998; 59: 81-84.

Mandal S, Kumar SS, Krishnamoorthy B, Basu SK. Development and evaluation of calcium alginate beads prepared by sequential and simultaneous methods. Brazilian Journal of Pharmaceutical Sciences. 2010; 46: 785-793.

Manjanna KM, Shivakumar B, Pramod Kumar TM. Formulation of oral sustained release aceclofenac microbeads. Int. J. Pharm. Tech. Research. 2009;1: 940-952.

Masareddy RS, Bolmal UB, Patil BR, Shah V. Metformin HCl loaded sodium alginate floating microspheres prepared by ionotropic gelation technique: Formulation, evaluation and optimization. Indian J. Novel Drug delivery. 2011; 2: 125-133.

Nappinnai M and Kishore VS. Formulation and evaluation of Diltiazem Hydrochloride microspheres. Indian J. Pharm. Sci. 2007; 69: 511-514.

Patil JS, Kamalapur MV, Marapur SC, Shiralshetti SS, Kadam DV. Ionotropically gelled chitosan-alginate complex hydrogel beads: Preparation, characterization and *in vitro* evaluation. Indian J. Pharm. Educ. Res. 2012; 46: 248-252.

Peh KK and Wong CF. Application of similarity factor in the development of controlled release diltiazem tablet. Drug Dev. Ind. Pharm. 2000; 26: 723–730

Rowe RC, Sheskey PJ and Owen SC. Handbook of Pharmaceutical excipients. 6th Ed. New York: The pharmaceutical press/ The American Pharmaceutical Association; 2009: 118-121.

Shirwaikar A, Annie S, Lakshmana Prabhu S, Aravind kumar G. Herbal excipients in novel drug delivery sytems. Indian J. Pharm. Sci. 2008; 70: 415-422.

Sultana Y, Mall S, maurya DP, Kumar D, Das M, Preparation and *in vitro* characterization of diltiazem hydrochloride loaded alginate microspheres. Pharm. Dev. Tech. 2009; 14: 321 – 331.

Swamy NGN and Abbas Z. Preparation and *In Vitro* Characterization of Mucoadhesive Polyvinyl Alcohol Microspheres Containing Amlodipine Besylate for Nasal Administration. Indian J. Pharm. Educ. Res. 2012; 46: 52-58.

Swamy NGN and Abbas Z. Mucoadhesive microspheres containing Amlodipine Besylate for nasal administration; improvised preparation and In vitro characterization. Indian Drugs. 2011; 48: 30-39

Swamy NGN, Rupa V, Abbas Z, Dasankoppa FS., Formulation and evaluation of Nanosuspensions for enhancing the dissolution of poorly soluble Mebendazole. Indian Drugs. 2010; 47: 47-54

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