RESEARCH PAPER

Formulation and Evaluation of Multi Particulate Extended-Release Dosage Form of Diltiazem HCl

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Abstract:

A multi-particulate extended-release dosage form of Diltiazem HCl was formulated and evaluated using drug layering technology to enhance dissolution and ensure controlled drug delivery. The study aimed to develop a stable and effective formulation with improved release characteristics. The prepared formulations were systematically evaluated for physicochemical and pre formulation parameters, including solubility studies, calibration curve analysis, FTIR, XRD, particle size distribution (PSD), flow properties of the API and granules, and drug–excipient compatibility through physical examination. Post-formulation evaluations such as mean filled capsule weight, lock length, and in vitro drug release studies of enteric-coated capsules were also performed, along with comparison of % drug release for optimized formulation (F2) against the Marketed preparation. The results indicated that the developed multi-particulate system was stable and exhibited satisfactory flow properties, compatibility, and controlled drug release behavior. The study concludes that the physicochemical properties and in vitro release profile of Diltiazem HCl formulations are significantly influenced by the choice of excipients, demonstrating the effectiveness of drug layering technology in developing extended-release dosage forms.

Key words: Diltiazem Hcl, Diltiazem HCl, drug layering technology, Lock length.

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Introduction:

Drug layering technology is an advanced multiparticulate formulation approach widely employed in the development of modified-release oral dosage forms. In this technique, active pharmaceutical ingredients are deposited onto inert starter cores such as sugar spheres or microcrystalline cellulose pellets through repeated spraying of drug solution or suspension under controlled processing conditions. This method allows precise control over drug loading and uniform distribution of the active ingredient, thereby improving dose accuracy and formulation reproducibility [1]. Drug layering is particularly advantageous for highly water-soluble drugs where direct compression or conventional granulation may present challenges in achieving controlled release.

The performance of drug-layered pellets depends on the physicochemical properties of the drug, binder selection, and process variables such as spray rate, inlet temperature, atomization pressure, and drying efficiency. Binders such as starch, polyvinylpyrrolidone, and hydroxypropyl methylcellulose are commonly used to improve adhesion of drug particles onto the pellet surface and prevent loss during processing [2]. Uniform deposition of the drug layer is essential because variations in layer thickness can directly influence drug release behavior and content uniformity. Therefore, careful optimization of formulation parameters is required to obtain pellets with desired quality attributes.

Drug layering technology also provides a flexible platform for applying functional polymer coatings to achieve sustained, delayed, or targeted drug release. After drug loading, polymeric films containing release-retarding agents such as chitosan, ethyl cellulose, or acrylic polymers can be applied over the pellets to regulate dissolution characteristics [3]. Plasticizers such as polyethylene glycol improve film flexibility, while opacifiers like titanium dioxide enhance coating stability and appearance. This multilayer design enables development of extended-release systems with predictable release kinetics and improved therapeutic efficiency.

Fluidized bed processing, is the most widely used technique for drug layering because it ensures efficient particle movement, uniform coating, and rapid solvent evaporation. The cyclic movement of pellets through the spray zone allows repeated deposition of thin uniform layers, minimizing agglomeration and improving batch consistency [4]. Compared with conventional granulation methods, drug layering offers superior control over pellet size, surface characteristics, and release performance, making it highly suitable for industrial-scale production of multiparticulate dosage forms.

Drug-layered multiparticulate systems offer several therapeutic advantages, including reduced dose dumping, uniform gastrointestinal distribution, lower local irritation, and flexibility in capsule filling or tablet compression. These systems are particularly useful for

drugs requiring extended-release delivery, as they maintain consistent plasma drug concentrations and reduce dosing frequency [5]. In addition, the multiparticulate nature decreases inter-patient variability in absorption and improves overall bioavailability compared with single-unit dosage forms. In the present study, drug layering technology was employed for the development of extended-release Diltiazem HCl capsules using sugar spheres as inert starter cores. Seal coating was performed using PVP K30, followed by drug loading with Diltiazem HCl and starch as binder. Extended-release coating was achieved using chitosan as the release-controlling polymer along with PEG 400 as plasticizer and titanium dioxide as opacifier. The objective was to optimize the formulation and process variables to obtain reproducible pellets with controlled drug release characteristics suitable for oral sustained delivery [6].

Material and Methods:

Materials

Diltiazem (Active Pharmaceutical Ingredient) was obtained as a gift sample from SD Fine-Chem Limited. Sugar spheres were procured from Colorcon. Polyvinylpyrrolidone (PVP K30) was supplied by Ashland. Starch was obtained from Loba Chemie, while chitosan was procured from Hi Media Laboratories. Polyethylene glycol 400 was supplied by BASF. Titanium dioxide was obtained from Tronox. Isopropyl alcohol was procured from BASF. Talc and Colloidal silicon dioxide were obtained from Imerys.

Methods :

Method of Preparation of Diltiazem HCl Capsules by Drug Layering Technology

Preparation of Starter Cores and Seal Coating

Sugar spheres were selected as inert starter cores because of their spherical shape, smooth surface, and suitability for uniform drug deposition. The sugar spheres were initially sieved to obtain a uniform size fraction and remove fines or oversized particles. A seal coating solution of PVP K30 was prepared in a suitable solvent system and applied onto the sugar spheres to improve surface strength and adhesion. The coated spheres were dried properly to obtain non-sticky seal-coated starter pellets.

Drug Layering of Diltiazem HCl

A drug layering solution was prepared by dissolving Diltiazem HCl in a suitable solvent with starch used as a binder to enhance adhesion. The seal-coated sugar spheres were loaded into the coating equipment and the drug solution was sprayed uniformly over the moving pellets. Controlled spraying conditions were maintained to ensure uniform drug distribution without agglomeration. The drug-loaded pellets were dried until a constant weight was achieved.

Extended-Release Polymer Coating

For sustained drug release, a coating solution containing chitosan as the release-retarding polymer was prepared. PEG 400 was incorporated as a plasticizer to improve film flexibility, while titanium dioxide was added as an opacifier to enhance coating stability and appearance. This polymeric coating was applied over the drug-layered pellets under controlled temperature and airflow conditions. The coated pellets were dried thoroughly to form a stable extended-release film around each pellet.

Lubrication, Filling and Evaluation

The dried coated pellets were blended with talc and colloidal silicon dioxide to improve flow properties and prevent sticking during capsule filling. The lubricated pellets were then accurately filled into hard gelatin capsules of suitable size. The prepared capsules were evaluated for flow properties, weight variation, drug content, and in vitro drug release characteristics. Preformulation studies including solubility, particle size distribution, and flow analysis were also performed to confirm suitability of the formulation process.

Table No:1 FORMULATION TABLE OF ENTERIC COATED CAPSULE OF DILTIAZEM HCL

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7
Seal coating:								
1	SUGAR SPHERES	52.0	52.0	52.0	52.0	52.0	52.0	52.0
2	POLYVINYLPYRROLIDONE (PVP K30)	3.0	3.0	3.0	3.0	3.0	3.0	3.0
3	PURIFIED WATER	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Seal coated pellets weight		**55.00**	**55.00**	**55.00**	**55.00**	**55.00**	**55.00**	**55.00**
Drug loading:								
4	DILTIAZEM HCL	118.0	118.0	118.0	118.0	118.0	118.0	118.0
5	Starch	13	26	26	26	26	26	26
6	PURIFIED WATER	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Drug loaded pellets weight		**186.00**	**199.00**	**199.00**	**199.00**	**199.00**	**199.00**	**199.00**
Extended-Release Coating:			**15%**	**15%**	**17%**	**19%**	**21%**	**23%**
7	Chitosan	20.50	21.07	18.29	20.76	23.23	25.70	28.17
8	POLYETHYLENE GLYCOL (PEG 400)	33.50	3.79	3.38	3.72	4.06	4.40	4.74
9	TITANIUM DIOXIDE	3.10	3.19	4.50	5.00	5.50	6.00	6.50
10	TALC	3.50	3.75	5.63	6.30	6.96	7.62	8.28
11	ISOPROPYL ALCOHOL (90%)	162.65	163.87	163.87	186.85	20.81	231.81	251.79
12	PURIFIED WATER (10) %	18.50	19.87	19.87	22.43	24.98	27.53	26.09
Extended- Release coated Pellets weight		**210.30**	**215.40**	**215.40**	**216.38**	**218.35**	**220.32**	**224.29**
Lubrication:								
13	TALC	1.0	1.0	1.0	1.0	1.0	1.0	1.0
14	COLLOIDAL SILICON DIOXIDE	0.600	0.600	0.600	0.600	0.600	0.600	0.600
Weight of Lubricated Pellets		**211.90**	**217.90**	**218.90**	**218.88**	**219.85**	**222.82**	**226.79**
Capsule Filling:								

RESULTS:

CALIBARTION CURVE FOR DILTIAZEM HCL:

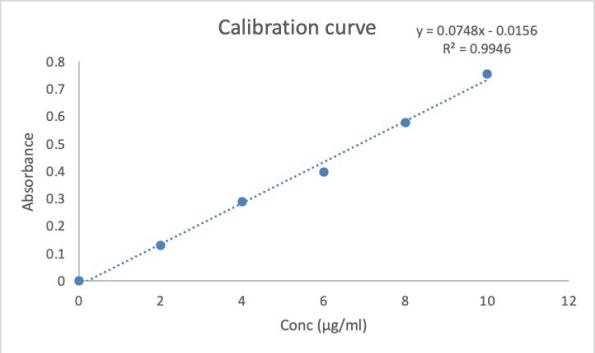

Fig No:1 Calibration curve for Diltiazem

The calibration curve shows a linear relationship between concentration and absorbance, indicating that absorbance increases proportionally as drug concentration increases.

FTIR(Fourier Transform Infrared Spectroscopy):

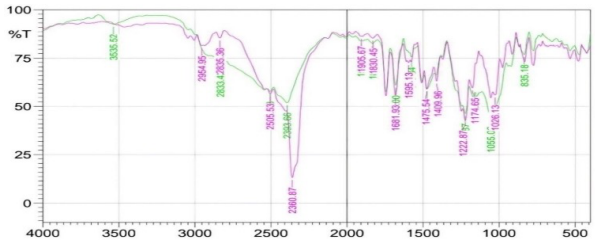

Fig No:2 FTIR SPECTRA OF Optimized Diltiazem HCL formulation

The FT-IR spectrum of Diltiazem HCl (API) and optimized formulation shows characteristic peaks corresponding to its functional groups. The broad band around 3500 cm^{-1} indicates O–H/N–H stretching, while peaks near 2950–2850 cm^{-1} represent aliphatic C–H stretching. A prominent peak in the region of 1680–1750 cm^{-1} confirms C=O stretching of ester groups. Peaks observed between 1600–1450 cm^{-1} are due to aromatic C=C stretching, and those around 1250–1000 cm^{-1} correspond to C–O stretching. The spectra of the drug and formulation show no significant shift or disappearance of peaks, indicating absence of drug–excipient interaction and good

EVALUATION TESTS :

Table:2 Mean Filled Capsule Weight

Batch	Mean Filled Capsule Weight	%RSD
F1	309.80±2.72	0.96
F2	305.72±2.70	0.90
F3	307.88±2.95	0.92
F4	311.85±3.00	0.93
F5	315.82±2.20	0.89
F6	320.90±3.10	0.93
F7	319.89±2.96	0.95

Assesses the uniformity of capsule dosage units by comparing the weight of individual capsules with the average weight to ensure consistent drug content.

Table:3 Results of Lock Length

Batch	Mean Lock Length (mm)±SD	%RSD
F1	18.29±0.39	1.95
F2	18.29±0.35	1.89
F3	18.32±0.38	2.12
F4	18.28±0.39	1.89
F5	18.29±0.39	1.87
F6	18.31±0.39	1.92
F7	18.25±0.39	1.96

Determines the proper sealing of the capsule by measuring the engagement between the cap and body, ensuring tight closure and preventing leakage

***IN VITRO* DRUG RELEASE STUDIES OF ENTERIC COATED CAPSULES**

Table:4 *In vitro* Drug Release profile of F1-F7 formulation

Time (hr)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	18	22	19	15	20	17	19
2	32	38	30	28	35	30	33
4	48	55	47	42	52	46	49
6	60	68	61	55	65	58	62
8	70	78	75	65	75	68	72
10	80	88	80	72	82	76	79
12	88	94	92	80	90	84	87

Dissolution Studies

ulation code	Zero order R^2	First order R^2	Higuchi model R^2	Korsmeyer-peppas model	
				R^2	n
F2	0.9476	0.9842	0.9944	0.6462	0.40

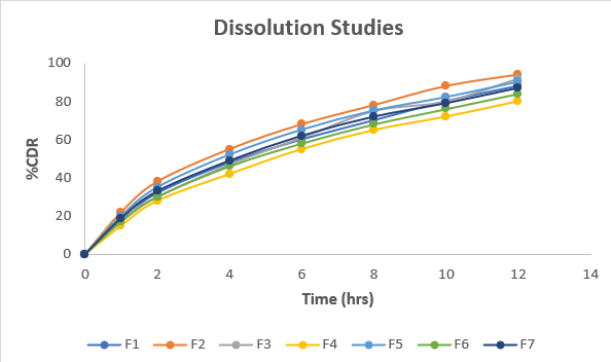

Fig3: Comparative Dissolution Rates of F1-F7

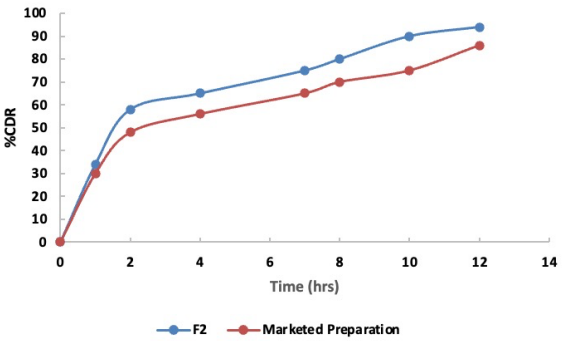

Fig No:4 Dissolution Profile of F2 and Marketed preparation

The *in vitro* drug release study of formulations F1–F7 demonstrated a controlled and extended-release pattern over a period of 12 hours, indicating the suitability of the multi-particulate system for sustained drug delivery. At the initial time point (1 hour), drug release ranged from 15% to 28%, suggesting a minimal burst release and effective coating of the pellets. As time progressed, all formulations showed a gradual increase in drug release, confirming controlled diffusion of Diltiazem from the coated particles.

Among the formulations, F2 exhibited the highest drug release, reaching 94 at 12 hours, indicating a comparatively faster release rate, possibly due to lower polymer coating thickness or higher permeability. In contrast, F4 showed the slowest release profile with 80% drug release at 12 hours, suggesting a stronger retardation effect. Formulations F2 and F5 demonstrated desirable release profiles with 94% and 90% drug release respectively at 12 hours, indicating a balanced extended-release behavior. Other formulations (F1, F6 and F7) showed moderate release patterns ranging between 84% and 88%.

KINETIC STUDY:

Table No:5 Kinetic study of Optimised Formulation

For formulation F2, the Higuchi model showed the highest R^2 value (0.9944) compared with Zero-order kinetics (0.9476), First-order kinetics (0.9842), and Korsmeyer–Peppas model (0.6462). This indicates that the drug release from formulation F2 predominantly follows the Higuchi diffusion model, meaning release occurs mainly by diffusion through the matrix. According to the Korsmeyer–Peppas n value = 0.40, the formulation follows Fickian diffusion (Case I transport) because for matrix tablets/cylindrical systems.

Based on the R^2 values, formulation F2 best fits the Higuchi model, meaning release occurs mainly by diffusion through the matrix.

Conclusion:

The purpose of this study was to develop an extended-release pellets of Diltiazem HCl under Biopharmaceutical classification system of class I classification. FTIR studies were carried out to select excipients for Diltiazem HCl extended-release pellets. Formulation F2 formulates extended-release pellets with assay, The in vitro drug release Diltiazem HCl extended-release pellets. formulation was found to be 94% after 12 hrs. In-vitro drug release studies closely indicate that best formulations obey Higuchi kinetics and the mechanism of drug release was by super case II transport. The study thoroughly evaluates the performance, consistency and efficiency of different formulations, ensuring that the most effective and reliable enteric-coated capsule is developed.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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45. + Raymond C Rowe, Paul J Sheskey and Sian C Owen, Hand Book of Pharmaceutical 5th edition. Excipient:782-784.