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Development of bilayer tablets using processed egg shell for sustained release indomethacine as immediate release component

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ABSTRACT

In this present study, it has been carried out to develop the Bilayer tablets of Processed eggshell powder as sustained release and Indomethacin as immediate release component. The prepared formulation satisfied both pre compression and post compression parameters. The compatibility studies were done by using FT-IR. Various sustained release formulations were formulated with HPMC K4M, K15M, K100M, polymer alone; and microcrystalline cellulose was used as diluents. The drug release data of dissolution studies of formulation f4 containing HPMC K100M is shown concentration levels were found to be 98.47% respectively.

Keywords: Bilayer Processed eggshell powder, Indomethacin, HPMC K4M, K15M, K100M.

ORAL DRUG DELIVERY

Despite phenomenal advances in the inhalable, injectable, transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred delivery route. There are of course many applications and large markets for non-oral products and the technologies that deliver them. However, if it is a viable option, oral drug delivery will be chosen in all but the most exceptional circumstances. Moreover, if the oral route is not immediately viable, pharmaceutical companies will often invest resources in making it viable, rather than plumping for an alternative delivery method [1--5].

Current Technologies in Oral Drug Delivery

Over the last 3 decades, many novel oral therapeutic systems have been invented along with the appreciable development of drug delivery technology. Although thede advanced DDS are manufactured or fabricated in traditional pharmaceutical formulations, such as tablets, capsules, sachets, suspensions, emulsions and solutions they are superior to the conventional oral dosage forms in terms of their therapeutic efficacies, toxicities and stabilities [6-10].

Based on the desired therapeutic objectifies oral DDS mat be assorted into 3 categories:

- Immediate release preparations.
- Controlled release preparations and

- Targeted release preparations.

a) Immediate release preparations:

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, anmtipyretics and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to elderly and bedridden and new business opportunities. Immediate release drug delivery system is a conventional type of drug delivery. It is designed to disintegrate and release their medicaments with no special rate controlling features 11-15.

These are the dosage forms in which ≥85% of labeled amount dissolves with in 30min. However for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix break up on contact with fluid in the stomach to allow the release the active drug which then become available in whole or in part, for absorption from GIT [16-17].

MECHANISM OF DRUG RELEASE

On exposure to aqueous fluids, hydrophilic matrices take up water and the polymer starts hydrating to from a gel layer. Drug release is controlled by diffusion barriers/by erosions. An initial burst of soluble drug may occur due to surface leaching when a matrix containing a swellable glassy polymer comes in to contact with an aqueous medium, there is an abrupt change from a glassy to rubbery state associate with swelling process with time, water infiltration deep in to a case increasing the thickness by the gel layer. The outer layer become fully hydrated and starts dissolving or eroding. When water reaches the centre of the system and the concentration of drug falls below the solubility value, the release rate of the drug begins to reduce. At the same time an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release.

MATERIALS AND METHODS

Preformulation studies

Physicocemical parameters

Organoleptic properties

The colour, odour and taste of the drug were recorded using descriptive terminology.

Melting point

Melting point of the drug was determined by capillary tube method. The melting point of Processed egg shell is 227.8^{o}C

Solubility study

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in Indian Pharmacopoeia 2007.

Loss on drying

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified condition. The accurately weighed 1gm of sample was transferred in glass-stoppered, shallow weighing bottle and accurately weighed the bottle. The bottle was transferred in oven and substance was dried at 105°C for 3 hours. The bottle was removed from oven and reweighed; loss on drying was calculated by following equation,

$$\mathbf{LOD} = \frac{\mathbf{Initial\ weight\ of\ substance - Final\ weight\ of\ substance}}{\mathbf{Initial\ weight\ of\ substance}} \times \mathbf{100}$$

Analytical methods

λ max Determination

The absorption maximum of the standard solution was scanned between 200-400 nm regions on Shimadzu-1700 UV spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

Preparation of standard graph of Processed egg shell

Preparation of solutions:

Preparation of 0.1N hydrochloric acid:

0.1N HCl was prepared according to I.P. 1996. A quantity of 8.5 ml of HCl was diluted with fresh distilled water to produce 1000 ml.

Preparation of stock solution of Processed egg shell:

Accurately weighed 20 mg of Processed egg shell was dissolved in little quantity of distilled water and volume was adjusted to 100 ml with the same to prepare standard solution.

Procedure:

From the stock solution, aliquots of 1, 2, 3, 4, 5, 6, 7, 8 ml were transferred to 100 ml volumetric flasks and final volume was made to 100 ml with 0.01N HCl. Absorbance values of these solutions were measured against blank (0.01N HCl) at 205.5nm using Shimadzu-1700 UV spectrophotometer.

Quantification of Drug

Accurately weighed 20 mg of Processed egg shell was dissolved in little quantity of distilled water and volume was adjusted to 100 ml with the same to prepare standard solution. From the above solution, aliquots of 5 ml were transferred to 100 ml volumetric flasks and final volume was made to 100 ml with 0.01N HCl. Absorbance values of these solutions were measured against blank (0.01N HCl) at 236nm using Shimadzu-1700 UV spectrophotometer.

Compatibility testing of drug with polymer

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product. Each polymer used in the formulations was blended with the drug levels that are realistic with respect to the final dosage form. Each polymer was thoroughly blended with drug to increase drug-polymer molecular contacts to accelerate the reactions if possible.

WET GRANULATION PROCEDURE

Sieving

All the ingredients were passed through the sieve#40 followed by the other ingredients were passed the same sieve.

Dry mixing

HPMC K100M, MCC, Aerosil, were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients.

Preparation of binder solution

- PVP

5% of PVP is prepared i.e.,5gm in 100ml of isopropyl Alcohol is added slowly by proper stirring for solution uniformity of binding solution

Granulation

The binder solution was added slowly to the dry mixed ingredients with constant mixing till to get solid mass to form uniform and optimum granules.

Drying

Then the wet granules were dried in Hot air oven samples were removed randomly at different time intervals from the total bulk of the granules and then checked out for moisture content

Sieving

The dried materials were passed through the sieve#22.Then magnesium stearate & Talc were added and compressed as sustained release tablet.

Direct Compression Method

All the ingredients were passed through the sieve#40 followed by the other ingredients were passed the same sieve. CCS, SSG, Cp, MCC, talc, were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients. Then the

granules were dried in Hot air oven samples were removed randomly at different time intervals from the total bulk of the granules and then checked out for moisture content. The materials were passed through the sieve#22.Then magnesium stearate, talc, Colouring agents were added and compressed as Immediate release tablet.

Method of preparation and characterization of powder blend

Table 1: Composition of Sustained release tablet formulation:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Processed egg shell	20	20	20	20	20	20	20	20	20
HPMCK4m	10	20	30						
HPMCK15m				10	20	30			
HPMCK100m							10	20	30
MCC	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Magnasium Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Total wt	120	120	120	120	120	120	120	120	120

*All the quantities are expressed as mg per tablet.

Table 2: Composition of Immediate release tablet formulation

Ingradients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Indomethacine	10	10	10	10	10	10	10	10	10
CCS	6.25	12.5	25						
SSG				6.25	12.5	25			
Cross Povidone							6.25	12.5	25
MCC	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Magnasium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total wt	100	100	100	100	100	100	100	100	100

*All the quantities are expressed as mg per tablet.

COMPRESSION OF POWDER BLENDS INTO TABLETS

After evaluation of powder blend Immediate release tablets and sustained release tablets were prepared by Direct Compression granulation method using (4mm diameter, round flat faced punches) multiple punch tablet compression machine. Each tablet contained 120mg of Processed egg shell and 100mg of Indomethacine, the batch size for each formulation was 10 tablets.

RESULTS AND DISCUSSION

Organoleptic properties

Odourless, white or almost white crystalline powder

Melting point

Melting point values of Processed egg shell powder sample was found to be in range of 185^0C to 189^0C. The reported melting point range for Processed egg shell powder is 183.5^0C to 184^0C. Hence, experimental values are in good agreement with official values.

Solubility study

Table 3: The solubility of Processed egg shell powder in various solvents

Name of solvent	Inference
Distilled water	Freely soluble
Methanol	Very soluble
Iso propyl alcohol	Soluble
Acetonitrile	Sparingly soluble
Acetone	Slightly soluble
Chloroform	Slightly soluble

Analytical methods

λ max Determination

The absorption maximum for Processed egg shell powder was found to be 237nm

Preparation of standard graph of Processed egg shell powder

Preparation of standard graph of Processed egg shell powder in 0.1N HCl.

UV absorption spectrum of Processed egg shell powder in 0.1N HCl shows λ max at 237nm. Absorbances obtained for various concentrations of Processed egg shell powder in 0.1N HCl are given in table no 6.2. The graph of absorbance vs concentration for Processed egg shell powder was found to be linear in the concentration range of 2-16 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-16 µg /ml.

Preparation of standard graph of Processed egg shell powder in p^H 6.8 Phosphate buffer

UV absorption spectrum of Processed egg shell powder in p^H 6.8 Phosphate buffer shows λ max at 238nm. Absorbances obtained for various concentrations of Processed egg shell powder in p^H 6.8 phosphate buffer are given in table no.6.3. The graph of absorbance vs concentration for Processed egg shell powder was found to be linear in the concentration range of 2-16 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-16 µg /ml.

Table 4: Data of concentration and absorbance for in Processed egg shell powder 0.1N HCl.

S.No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	2	0.118
3	4	0.276
4	6	0.452

5	8	0.796
6	10	0.982
7	12	1.089
8	14	1.181

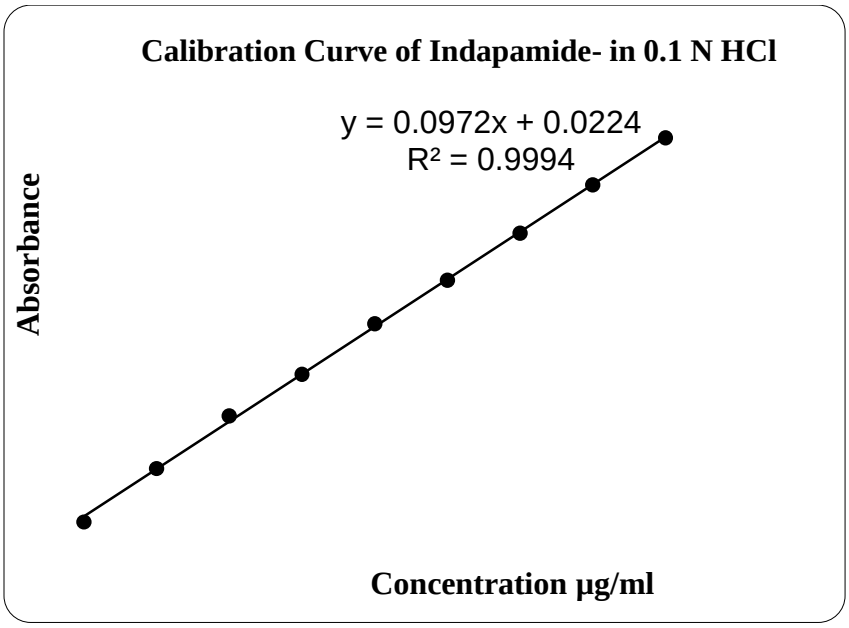

Figure 1: Standard graph of Processed egg shell powder 0.1N HCl

Table 5: Data of concentration and absorbance for Processed egg shell powder pH 6.8 phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	2	0.121
3	4	0.267
4	6	0.471
5	8	0.692
6	10	0.875
7	12	1.097
8	14	1.175

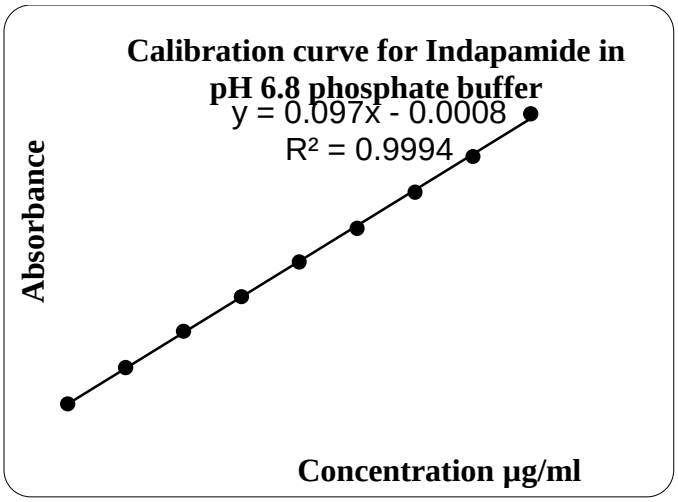

Figure 2: Standard graph of Processed egg shell powder in 6.8 buffer

Preparation of standard graph of Indomethacin in p^H 6.8 Phosphate buffer

UV absorption spectrum of Indomethacin in p^H 6.8 Phosphate buffer shows λ max at 286nm. Absorbances obtained for various concentrations of Indomethacin in p^H 6.8 phosphate buffer are given in table no.6.3. The graph of absorbance vs concentration for Indomethacin was found to be linear in the concentration range of 2-8 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-8µg /ml.

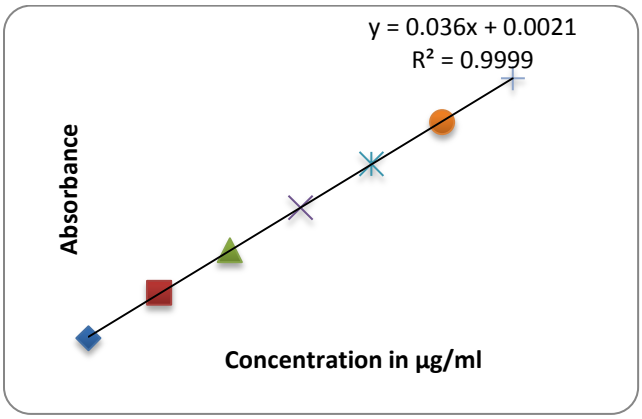

Figure 3: Standard graph of Indomethacin in phosphate buffer

Percentage purity of pure Drug

The percentage purity of drug was calculated by using calibration graph method (least square method).

Table 15: Percentage purity of pure drug

S. No.	Percentage purity (%)	Percentage purity (%)
1	100.60	101.50

2	99.08	98.62
3	99.40	99.54
Avg purity	99.69	99.88

The reported percentage purity is 98 to 102% (I.P. 1996).

Characterization of powder blend (SR and IR)

The powder blends were prepared by mixing of various ingredients mentioned in table and used for characterization of various flow properties of powder.

Table 6: preformulation parameters of sustained release formulation

Formulation code	Angle of Repose (θ)	Bulk Density(g/ml)	Tapped Bulk Density(g/ml)	Carr's Index (%)	Hausner's Ratio
F1	22.90	0.459	0.534	14.04	1.16
F2	24.38	0.479	0.548	12.59	1.14
F3	20.35	0.464	0.528	12.22	1.14
F4	23.14	0.480	0.564	13.30	1.15
F5	23.90	0.439	0.514	12.83	1.13
F6	21.20	0.449	0.521	13.82	1.16
F7	22.34	0.465	0.523	14.02	1.17
F8	23.01	0.453	0.517	13.92	1.15
F9	22.87	0.526	0.527	14.23	1.14

Table 7: preformulation parameters of immeadiate release formulation

Formulation	Angle of repose	Bulk density	Tapped density	Carrs index	Hausner's Ratio
F1	26.81	0.43	0.53	17.28	1.12
F2	29.73	0.45	0.54	13.44	1.14
F3	27.54	0.49	0.56	15.69	1.13
F4	25.61	0.45	0.54	17.76	1.15
F5	28.64	0.43	0.58	14.69	1.12
F6	27.73	0.45	0.54	15.44	1.14
F7	26.27	0.46	0.53	14.18	1.15
F8	26.35	0.47	0.58	15.17	1.14
F9	25.87	0.43	0.54	14.23	1.15

Bulk Density (BD)

The powder blends of formulations have the bulk density ranged between Sustained Release Formulations-0.439±0.0005 to 0.526±0.005 gm/ml, Immediate Release Formulations-0.43to0.49gm/ml.

Tapped bulk density (TBD)

The powder blends of formulations have the tapped bulk density ranged between Sustained Release Formulations-0.867±0.0005 to 0.898±0.001 g/ml Immediate Release Formulations-0.53-0.58, These values indicate good packing characteristics and the powder was not bulky.

Carr's Compressibility Index

The carr's index for all the both formulations was found to 12-18%indicating that the powders have a excellent compressibility.

Hausner's Ratio

The hausner ratio for all the both formulations was found to be <1.25, indicating good flow properties.

Angle of repose

The flow properties of granules were analyzed by determining angle of repose which was found to be between Sustained Release Formulations- 20.07 to 22.1, Immediate Release Formulations-25.61-29.73. Excellent flow property.

EVALUATION OF SUSTAINED RELEASE TABLET

Appearance

The tablets were observed visually and did not show any defect such as capping, chipping and lamination.

Physical characteristic

The physical characteristic of Processed egg shell powder tablets (F1 to F9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations (F1 to F9) found to be within the limits specified in official books.

Table 8: Physico-chemical characterization of Processed egg shell powder tablets:

S.no	Formulation	Weight variation	Thickness	Hardness	Friability	Disintegration Time
1	F1	0.398	1.5	4	0.26	0.26
2	F2	0.415	1.6	4	0.62	0.62
3	F3	0.395	1.7	4.5	0.78	0.78
4	F4	0.413	1.6	4	0.79	0.79
5	F5	0.407	1.5	4.5	0.41	0.41
6	F6	0.386	1.6	4	0.38	0.38
7	F7	0.394	1.5	4	0.35	0.35
8	F8	0.405	1.6	4.5	0.36	0.36
9	F9	0.412	1.5	4.5	0.29	0.29

Table 9 : Physico-chemical characterization of Indomethacin tablets

Sno	Formulation	Weight variation	Thickness (mm)	Hardness (Kg/Cm^2)	Friability %	Disintegrating Time (sec)
1	F1	0.472	2.1	2.8	0.34	43
2	F2	0.765	2.1	2.6	0.37	47
3	F3	0.646	2.3	2.9	0.27	53
4	F4	0.629	2.3	2.6	0.32	40
5	F5	0.685	2.3	2.5	0.43	34
6	F6	0.704	2.2	2.8	0.34	43
7	F7	0.698	2.2	2.6	0.37	45
8	F8	0.712	2.1	2.5	0.34	47
9	F9	0.694	2.2	2.6	0.37	49

Dimension (Thickness and Diameter)

Thickness and diameter specifications may be set on an individual product basis. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. The size (diameter) of the tablets of all formulations were found to be 4.0±0.0 mm and thickness ranged between 2.10to 2.18.

Tablet Hardness

A difference in tablet hardness reflects difference in tablet density and porosity. Which in turn are supposed to result in different release pattern of the drug by affecting the rate of penetration of dissolution fluid at the surface of the tablet and formation of gel barrier. The hardness of tablets was found to be in the range of 4 kg/cm^2 to 4.5 kg/cm^2. This indicates good tablet strength.

Percent Friability

Percentage friability of all the formulations was found between 0.284±0.008 to 0.454±0.054%. This indicated good handling property of the prepared SR tablet.

Weight Variation

A tablet is designed to contain a specific amount of drug. When the average mass of the tablet is 350 mg the Pharmacopoeial limit for percentage deviation is ± 5 %. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the Pharmacopoeial specifications.

Drug content of Processed egg shell powder

The content of active ingredients in the formulation was found to be between 98.54±1.7 to 100.86±1.2 % w/w, which is within the specified limit as per IP 2007(i.e. 90-110% w/w).

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6.2.5. *In-vitro* dissolution studies

Table 10: Dissolution data of formulations

Time (hours)	Dissolution medium	% Drug release of F1	% Drug release of F2	% Drug release of F3	% Drug release of F4	% Drug release of F5	% Drug release of F6	% Drug release of F7	% Drug release of F8	% Drug release of F9
0	0.1 N HCl	0	0	0	**0**	0	0	0	0	0
0.5		12.43	5.16	3.16	**5.89**	13.46	5.12	3.79	8.56	13.49
1		21.65	13.46	9.19	**11.29**	25.54	11.25	9.46	18.64	23.76
1.5		30.21	2079	15.46	**24.57**	31.48	19.21	16.48	26.79	31.49
2		40.77	31.48	22.78	**31.87**	38.49	25.89	27.64	34.67	44.19
3		46.10	46.19	29.16	**39.46**	45.76	36.19	35.57	44.59	50.73
4		54.69	59.87	38.46	**45.21**	57.49	45.73	43.58	57.19	64.18
5	pH 6.8 phosphate bufffer	65.87	67.46	44.59	**52.34**	66.87	56.79	56.78	64.28	74.46
6		75.63	78.46	50.76	**60.79**	79.47	62.49	69.47	79.49	88.46
7		83.61	88.76	60.46	**65.16**	88.87	70.23	75.89	88.46	99.91
8		95.89	-	65.16	**72.46**	100.78	79.45	85.46	99.76	-
9		100.69	-	69.46	**80.77**	-	87.74	99.46	-	-
10		-	-	72.46	**98.47**	-	98.16	-	-	-

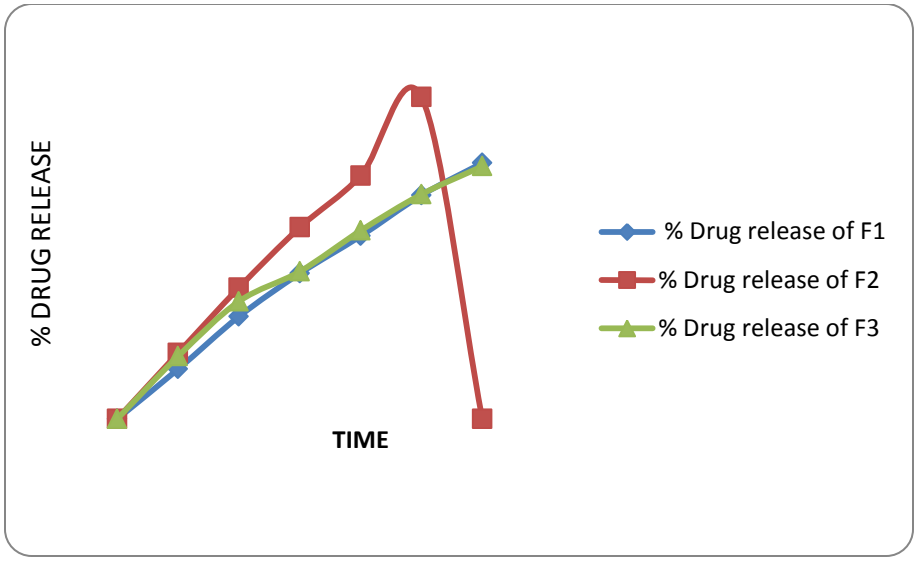

Figure 4: % drug release of formulation F1,F2,F3

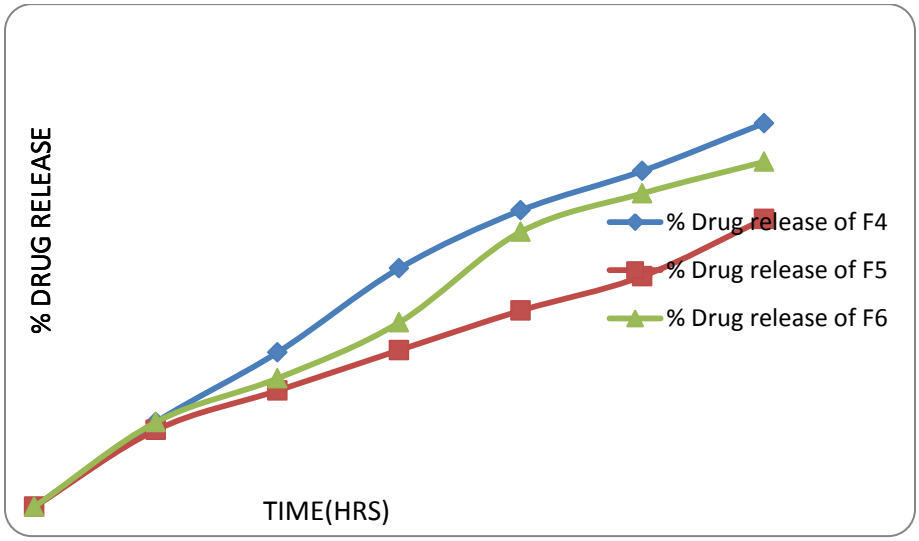

Figure 5: % drug release of formulation F4, F5, F6

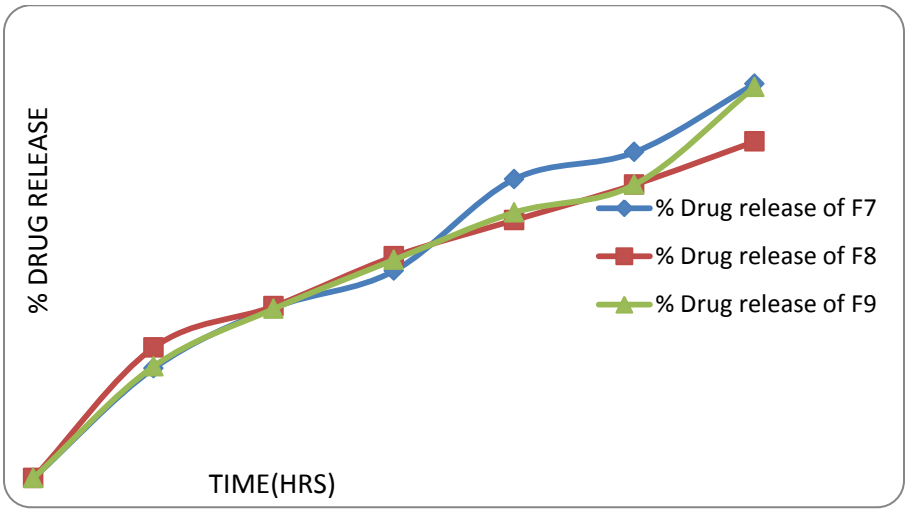

Figure 6: % drug release of formulation F7, F8, F9

Various sustained release formulations were formulated with HPMC K4M, K15M, K100M, polymer alone; and microcrystalline cellulose was used as diluents. The drug release data of dissolution studies of formulation f4 containing HPMC K100M is shown concentration levels were found to be 98.47% respectively.

Kinetics of *In-vitro* Drug Release

The drug diffusion through most type of polymeric system is often best described by Fickian diffusion (diffusion exponent, n=0.5), but other process in addition to diffusion are important. There is also a relaxation of the polymer chain, which influences the drug release mechanism. This process is described as non- fickian or anomalous diffusion (n=0.5-1.0). Release from initially dry, hydrophilic glassy polymer that swell when added to water and become rubbery, show anomalous diffusion as a result of the rearrangement of macromolecular chain. The thermodynamics state of the polymer and penetrant concentration are responsible for the different type of the diffusion. A third class of diffusion is case-II diffusion (n=1), which is a special case of non- Fickian diffusion. To obtain kinetic parameter of dissolution profile, data were fitted to different kinetic models.

Table 11: Different kinetic models for Processed egg shell powder Multi-Particulate Mini tablets

Code	Zero order		First order		Higuchi		Peppas		Best fit model
	R^2	K_0 mg/h^{-1}	R^2	K_1 (h^{-1})	R^2	K (mg $h^{-1/2}$)	R^2	n	
F8	0.9786	3.769	0.9349	0.1938	0.9732	23.8548	0.9437	1.9166	Peppas

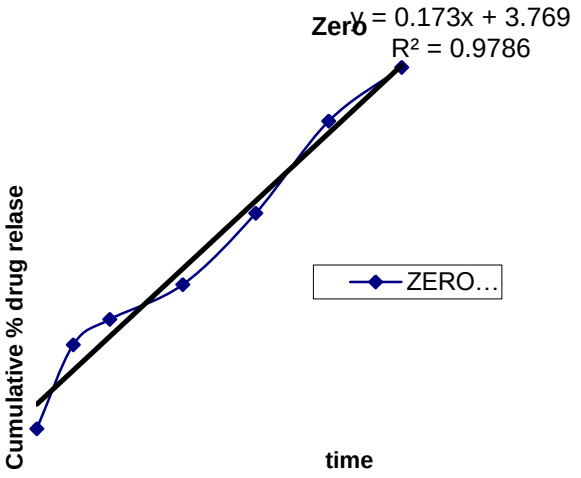

Figure 6: Zero order release

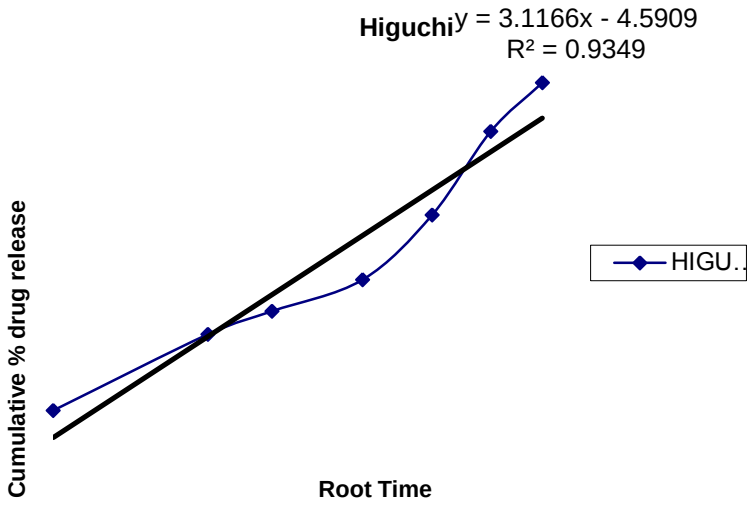

Figure 7: First order release

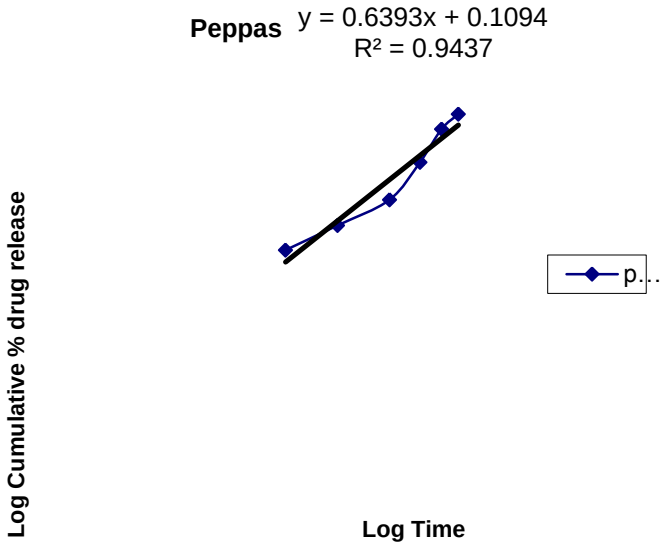

Figure 8: Higuchi plot

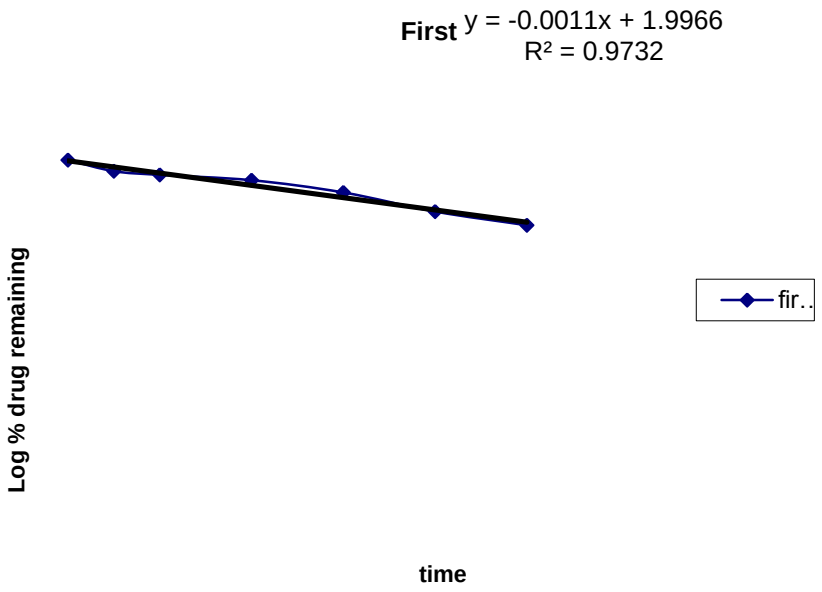

Figure 9: Peppas model

Drug content of Processed egg shell powder

The content of active ingredients in the formulation was found to be between 98.54±1.7 to 100.86±1.2 % w/w, which is within the specified limit as per IP 2007(i.e. 90-110% w/w).

In-vitro dissolution studies

Table 12: Dissolution data of formulations

Time (Min.)	% Drug release of F1	% Drug release of F2	% Drug release of F3	% Drug release of F4	% Drug release of F5	% Drug release of F6	% Drug release of F7	% Drug release of F8	% Drug release of F9
0	0	0	0	0	0	0	0	0	0
5	15.46	20.46	19.47	21.48	19.48	21.48	24.76	29.43	25.19
10	31.79	40.76	36.49	39.15	29.46	32.57	38.41	38.74	38.17
15	45.17	59.47	45.78	60.46	39.72	46.73	46.73	49.97	49.22
20	56.78	75.49	58.47	75.16	49.75	69.73	67.41	58.16	59.9
25	69.47	99.97	69.74	85.16	58.46	79.47	73.49	66.19	66.17
30	79.48	-	78.46	97.25	72.97	87.46	88.87	75.88	88.19

Various sustained release formulations were formulated with super disintegrants, polymer alone; and microcrystalline cellulose was used as diluents. The drug release data of dissolution studies of formulation f4 containing is shown concentration levels were found to be 98.16% respectively.

Compatability studies

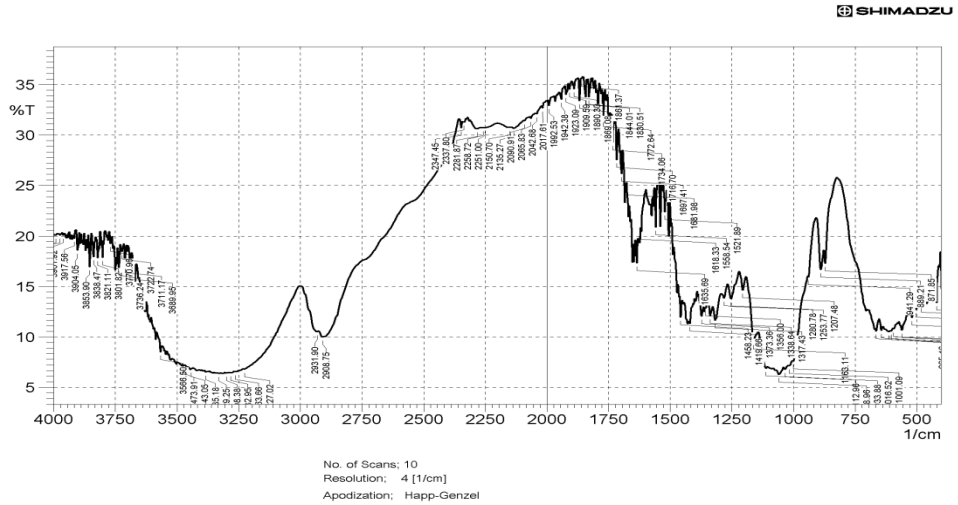

Figure 10: FTIR spectrum of pure drug

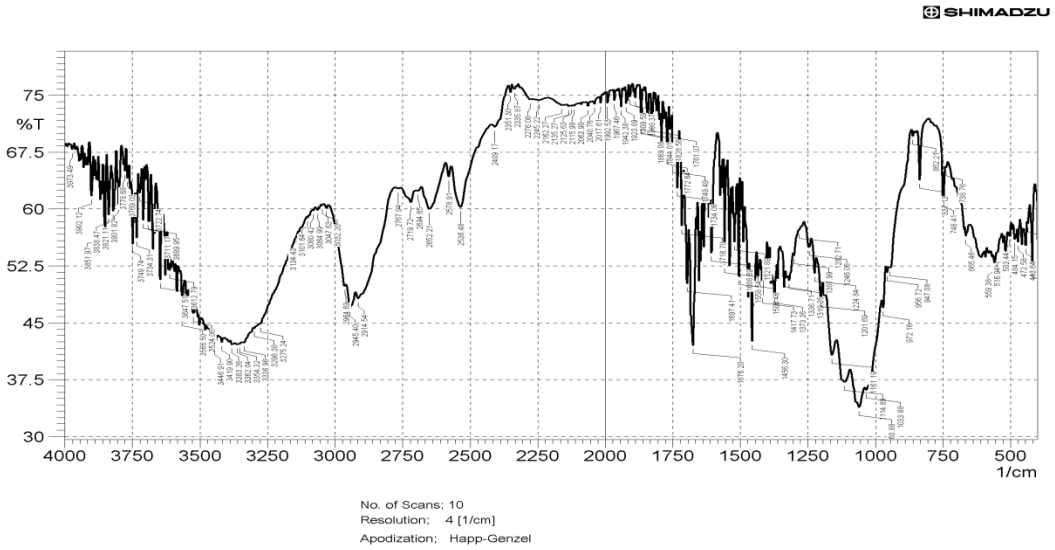

Figure 11: FTIR spectrum of optimized formulation

CONCLUSION

In this context, it has been concluded that the formulations of Processed egg shell powder sustained pellets in this investigation was found to be satisfactory based on *in vitro* release studies. Thus the objectives envisaged in this research work have been achieved. The bioavailability of the drug can also be improved with this sustained drug delivery system which increases efficacy, compliance and better clinical usefulness of patients.

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